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Kinematic Alignment and Total Knee Arthroplasty

Hugh Benedict Waterson

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Abstract

Osteoarthritis (OA) is one of the leading causes of global disability. Surgical intervention in the form of Total Knee Arthroplasty (TKA) has been established as an excellent treatment modality for people with OA who experience joint symptoms that have a substantial impact on their quality of life and are refractory to non-surgical treatment. In the 1970s the concept of implanting TKAs in mechanical alignment (MA) was developed as a compromise to confer mechanical advantage to the prosthesis, ignoring the patient's natural anatomy, to prevent early failure of the implant. Until now, this compromise has not been revisited. Satisfaction following TKA remains inferior to total hip arthroplasty. The cause of this dissatisfaction is not clear. Implant survival is no longer comparable to that of the early designs of TKA, and recent studies have suggested that deviation from neutral alignment does not have the detrimental effect on survivorship as previously thought.

In an attempt to improve patient satisfaction following TKA a new technique has been developed whereby the prostheses are implanted in such a way as to recreate the alignment of the knee in the patient's pre-arthritic state. This has been termed natural or kinematic alignment (KA). This thesis examines the impact of KA in TKA with the primary hypothesis that TKA performed utilising KA would lead to improved functional outcome following surgery compared to that of MA.

An initial single surgeon proof of concept case series of 25 patients was performed to look at the precision of new patient specific cutting blocks. The results suggested that

the cutting blocks were accurate in producing the desired cuts. Following the proof of concept case series, a feasibility study was then performed comparing the new KA technique with the standard MA technique. The feasibility study familiarised the operating surgeons with the new technology in preparation for a Randomised Control Trial (RCT).

A prospective blinded RCT was performed to compare the functional outcome of patients implanted with TKA in MA with that of KA. A total of 71 patients undergoing TKA were randomised to either MA (n=35) or KA (n=36). Pre- and post-operative hip knee ankle (HKA) radiographs were analysed. A number of patient reported outcome measures and functional tests were assessed pre-operatively, 6 weeks, 3 months, 6 months, and at 1 year post-operation. The cutting guides were accurate. There were no statistically significant differences between the MA and KA groups at 1 year.

A cohort of post-menopausal women with unilateral osteoarthritis treated with TKA utilising the KA philosophy had dual energy x-ray absorptiometry scans 1.5 years post-operatively using a modified validated densitometric analysis protocol, to assess peri-prosthetic Bone Mineral Density (BMD). The contralateral knee was scanned so that relative bone mineral density could be calculated. Statistical analysis revealed no significant difference in relative peri-prosthetic bone mineral density due to variation in implant position with respect to the Lateral Distal Femoral Angle (LDFA) and the Medial Proximal Tibial Angle (MPTA). There was a significant correlation with overall HKA angle and the relative BMD under the medial side of the tibial tray.

KA TKAs appear to have comparable short-term results to MA TKAs with no significant differences in function 1 year post-operatively. Overall HKA angle rather than the individual component position caused change in relative BMD under the tibial tray, therefore aiming for an anatomical joint line may improve kinematics without a detrimental effect on the implant. Further research is required to see if any theoretical long-term functional benefits of KA are realised or if there are any potential effects on implant survival.

Lay Summary

Total knee replacement surgery for osteoarthritis of the knee is a common procedure. Over 80,000 knee replacements were performed in the UK in 2016. About 85% of patients who have a total knee replacement are satisfied with the outcome of their surgery. This leaves a minority of patients who are not happy with their knee replacement. This thesis examines a new technique for implanting knee replacements in a slightly different way to what has been the convention over the last 20 years. The theory was that trying to implant the knee replacement in such a way that it more closely resembled the patients own anatomy would improve patient satisfaction following surgery. The results from the various studies in this thesis, in fact demonstrated no difference in outcome between the new technique and what was previous standard practice.

Declaration

I hereby declare that all work contained within this thesis was undertaken by me alone, except where explicitly stated otherwise. The material within the thesis has not been submitted elsewhere as part of other degree or professional qualifications.

Ben Waterson

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Glossary of Abbreviations

AKSS- American Knee Society Score

BMD- Bone Mineral Denisty

CN- Computer Navigation

DEXA- Dual Energy X-ray Absorptiometry

EQ5D- EuroQol-five dimensions

FEA- Flexion and Extension Axis

HKA- Hip-Knee-Ankle

KA- Kinamtic Alignment

KOOS- Knee Injury and Osteoarthritis Outcome Score

LDFA- Lateral Distal Femoral Angle

LLR- Long Leg Radiographs

MA- Mechanical Alignment

MCID- Minimal Clinically Important Difference

MPTA- Medical Proximal Tibial Angle

NJR- National Joint Registry

NOA- Neutral Overall Alignment

OA- Osteoarthritis

PROMs- Patient Reported Outcome Measures

PSI- Patient Specific Instrumentation

RCT- Randomised Control Trial

ROI- Regions Of Interest

TKA- Total Knee Arthroplasty

UCLA- The University at Los Angles Activity Score

Chapter 1 Introduction, Scope and Outline

1.1 Introduction

Osteoarthritis is a highly disabling disease affecting the joints of the body. The pathogenesis of OA appears to be the result of a complex interplay between mechanical, cellular and biochemical forces. It is estimated that 10–12% of the adult population has symptomatic OA (Dunlop et al. 2001). The disease causes a huge amount of disability with the risk of OA affecting mobility reported to be greater than any other medical condition in people aged 65 and over (Guccione et al. 1994; Hunter 2011). In the estimates for the Global Burden of Disease study, OA is eighth in the list of worldwide causes of disability (Lopez & Murray 1998), as measured by years of life lived with a disability.

There is a spectrum of treatment for OA. Surgical intervention in the form of TKA should be considered for people with OA who experience joint symptoms (pain, stiffness and reduced function) that have a substantial impact on their quality of life and are refractory to non-surgical treatment (NICE 2012).

The number of TKAs performed in the UK has been increasing year on year with excess of 100,000 being recorded by the national joint registry of England, Wales and Northern Ireland in 2017 (NJR 2017). The 10 year revision risk for cemented, unconstrained fixed bearing TKA is just over 3% (NJR 2017). TKA is now a more

common procedure than total hip arthroplasty but patient satisfaction following TKA surgery remains inferior (Wylde et al. 2009; Bourne et al. 2010; Baker et al. 2012). Patient expectation, Body Mass Index (BMI), age and depression have been identified as causes of dissatisfaction (Bourne et al. 2007) but there still remains a small percentage of patients where the reason for a poor outcome following surgery is not clear. The knee is a complex joint involving movement in 6° of freedom and errors in alignment of the implant can lead to alteration in knee kinematics that could compromise patient outcome.

The concept of mechanical alignment (MA) was developed by Insall (Insall et al. 1996). Prostheses were implanted in such a way as to distribute load evenly across the joint. This was an attempt to improve survivorship of the early rudimentary designs of TKA by conferring mechanical advantage to the implant. MA ignores the patient's natural alignment. Due to the limitations in prosthesis design and accurate alignment analysis, the success of a TKA has historically been measured by implant survivorship, largely attributed to implant alignment in the coronal plane. Surgeons have had to rely on radiographs to analyse alignment. As a result of this, a disproportionate amount of research has focused on alignment in the coronal plane only and the relationship the implant has to the mechanical axis. Deviation from neutral overall alignment (NOA) in the coronal plane has previously been thought to contribute to reduced survivorship of the implant (Bargren et al. 1983; Berend et al. 2004; Morgan et al. 2008; Fang et al. 2009). As a consequence, recent technology has focused on ways to reproduce more accurately NOA. Computer navigation was one such innovation that improved the accuracy of alignment (Brin et al. 2010; Pang

et al. 2011), but this has not been translated into improvement in functional outcome or patient satisfaction (Matziolis et al. 2010; Spencer et al. 2007; Stulberg et al. 2006). Current data from the national joint registries demonstrates that implant survivorship has significantly improved when compared to early designs (NJR 2017) and recent research has suggested that deviation from NOA does not have a detrimental effect on implant survivorship as previously thought (Matziolis et al. 2010; Parratte et al. 2010; Bonner et al. 2011).

Improvements in imaging have led to an increased understanding and appreciation of alignment in TKA by being able to assess the joint in three dimensions.

Computerised tomography (CT) is now recognised as being the most accurate way of assessing alignment (Hirschmann et al. 2011). The concept of what constitutes normal alignment has been revisited and it has been demonstrated that 32% of men and 17% of women have constitutional varus knees (Bellemans et al. 2012). The use of more detailed imaging has called into question established reference landmarks regarding alignment. Eckhoff's studies of the knee concluded that the axis of the leg is not straight and the true flexion and extension axis does not correspond with the eipcondylar axis (Eckhoff et al. 2007; Eckhoff et al. 2003; Eckhoff et al. 2005; Eckhoff et al. 2001). The use of both Magnetic Resonance Imaging (MRI) and CT imaging modalities has also lead to the development of patient specific instrumentation (PSI). Computer software is used to create a 3-dimensional reconstruction of the patient's knee from which custom fit cutting blocks are produced to assist the surgeon in making their desired femoral and tibial cuts.

The concept of trying to implant the prosthesis in such a way as to recreate the limb alignment in the pre-arthritic state has been termed natural or kinematic alignment (KA). This thesis aims to examine the concept of KA and study the potential implications in terms of patient reported outcomes and functional outcomes in patients who receive TKA implanted in KA compared to conventional MA.

1.2 Scope of the thesis and research hypothesis

The first aim of the thesis was to investigate thoroughly the use of a new technology in TKA, that of the Triathlon® Knee System with Otismed® ShapeMatch® PSI aiming for KA. This technique for TKA not only uses a new approach with regards PSI but employs an entirely new alignment philosophy in TKA. The primary hypothesis was that TKA performed utilising the KA philosophy would lead to improved functional outcome following surgery

The second component of the thesis was to examine the way we assess outcome following surgery. By setting up a functional laboratory the aim was to quantify accurately patient performance with dynamic testing and look at the correlation between actual function and results from patient reported outcome questionnaires. The secondary hypothesis was that there would be no difference between PROMs and quantified functional performance tests.

With the use of new this technology there are specific research questions that require answering:

1. In an initial proof of concept study, does the new computer software that predicts the alignment of their knees in the pre-morbid state, conform with the population study by Bellemans et al (Bellemans et al. 2012)?
2. How reliable are the patient specific cutting blocks in achieving the desired knee alignment?
3. Does implanting the prosthesis in KA improve the functional outcome following TKA?
4. Does the standard method of assessment through patient reported outcome questionnaires correspond to the patient's actual levels of function?
5. What effect does deviation from overall neutral mechanical alignment have on the bone density surrounding the implant?

1.3 Outline

Chapter 2 is a review of the literature relating to alignment in TKA. In order to understand why MA has become a fundamental tenet of knee surgery, an historical appreciation of the rudimentary designs of TKA is required. This chapter looks at the evidence related to alignment and implant survivorship and examines if there is scope to deviate away from the mechanical alignment philosophy. Methods for assessing patient outcome following surgery are also addressed. The literature

relating to patient specific instrumentation and KA is reviewed as well as previous studies looking into the impact of TKA on BMD around the knee.

Chapter 3 documents the proof of concept study of 25 patients who received the new technology. The pre-operative radiographs and MRI plans produced from Otismed® ShapeMatch® technology (Stryker Corporation, Mahwah, NJ, USA, FDA clearance) are examined and compared to the post-operative radiographs to assess the accuracy of Otisknee™ custom cutting guides (Stryker Corporation, Mahwah, NJ, USA, FDA clearance).

Chapter 4 is a feasibility study investigating the next cohort of patients who received MRI scans of the knee who then went on to have their TKA implanted in KA; the feasibility study was used to familiarise the surgeons with the operative technique. It compares KA with the standard TKAs in MA that were being used in the unit at the time. Patient outcomes in the form of the Western Ontario & McMaster Universities Arthritis Index (WOMAC) and Oxford Knee Score (OKS) scores are compared between the KA and MA cohorts. The aim of the feasibility study was to aid and instruct on the planning the RCT that was to follow.

Chapter 5 is an RCT comparing Otismed® ShapeMatch® technology (Stryker Corporation, Mahwah, NJ, USA, FDA clearance) and Otisknee™ custom cutting guides (Stryker Corporation, Mahwah, NJ, USA, FDA clearance) to implant TKAs

in KA with conventional TKAs implanted in MA. The study looked at patient outcomes, examining and comparing patient reported outcome measures with functional assessment of patient performance.

Chapter 6 examines the impact of different alignments on Bone Mineral Density around the femoral and tibial components in TKA using Dual Energy X-ray Absorptiometry (DEXA).

Chapter 7 is the final chapter of the thesis and reflects upon what conclusions can be drawn from the research. It outlines my future research plans on the subject of KA.

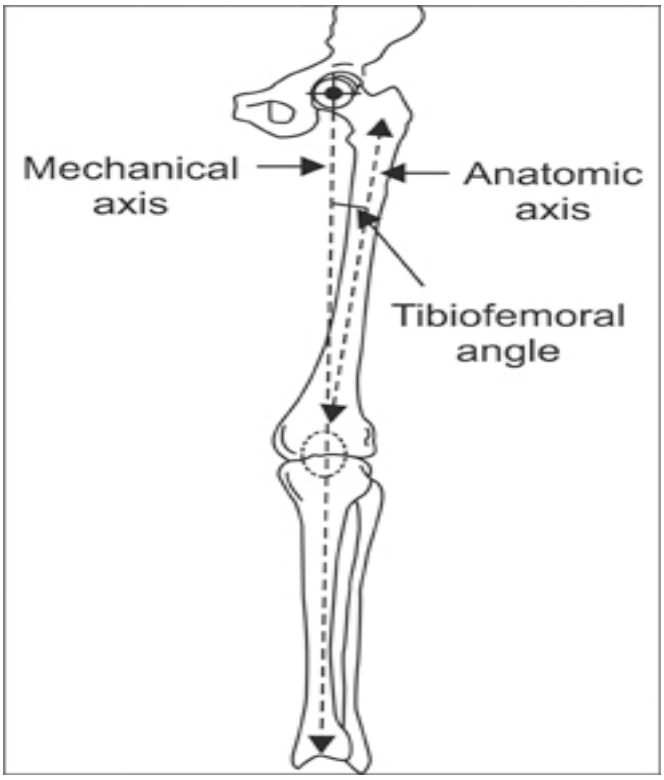
Chapter 2 Literature Review

2.1 History of Alignment in Total Knee Arthroplasty

Anatomists started detailing the morphology of the knee in the mid 1800s. The concept of improving lower limb alignment through osteotomy can be traced back to 1875 when Volkmann wrote on tibial osteotomies to improve a deformity of the knee (Pinskerova et al. 2000). Zuppinger carried out the first radiographic study of the knee in 1904 (Zuppinger 1904). Early osteotomies concentrated on straightening the leg and distributing load symmetrically across the joint. Debeyre and Patte were the first to report on a series of corrective osteotomies in osteoarthritis of the knee concluding that they redistributed the load across the joint (Scott 2006).

By the mid 20th century radiographs were becoming more widespread in clinical work and consequently various angles around the knee could be measured. The term 'femorotibia angle' was coined as the measurement of the intersection in the coronal plane of the long axis of femur and tibia at the knee joint and today is often referred to as the tibiofemoral angle (Figure 2.1). This angle gained popularity in knee osteotomies as a way of determining the degree of correction. The first published paper in the UK to reference the femorotibial angle in osteotomies was by Jackson and Waugh in 1961 (Jackson & Waugh 1961), and measured 50 healthy knees and found the femorotibial angle to be 2°. Kettelkamp et al. later disputed this figure in 1976 and suggested that the normal femorotibial valgus angulation was 7° (Kettelkamp et al. 1976), which is more in line with what we accept today.

Figure 2.1 Image showing the relationship between the mechanical and anatomical axis illustrating the tibiofemoral angle.



The concept of the mechanical axis was introduced around the same time in Maquet's 'Quelques remarques sur la radiographies' (De Marchin et al. 1963). Alignment correction operations were planned on the basis of measurements made from full length X-rays of the affected leg, taken with the patient balancing on that extremity demonstrating an angle formed by the mechanical axis of the femur, connecting the centre of the femoral head and the inter-condylar notch and the mechanical axis of the tibia between the tibial spines and the centre of the ankle.

The earliest techniques in TKA can be traced back to 1890s. Theophilus Gluck implanted an ivory, hinged TKA fixed with plaster of Paris and colophony. The first metallic mould was introduced into the knee as a primitive form of arthroplasty by Campbell in 1940 (Campbell 1988). In 1951 Dr Waldius deveopled a hinged TKA made of acrylic that was modified to cobalt chrome in 1958 (Ranawat 2002). Attempts were made to correct alignment with the acrylic tibial plateau prostheses by MacIntosh also in 1958 (Macintosh 1958). Dr Walduius' prosthesis was in use until the 1970s along with a number of other hinged designs.

In the 1960s two significant materials were developed for use in orthopaedics. The use of methyl-methacrylate as a fixation grout began in 1960 and in 1963 high-density polyethylene plastic was introduced as a bearing surface. It was not until the 1970s though that the prototypes for the TKAs in use today were developed

The early condylar total knee designs of the 1970s fell into two broad categories; the anatomic approach and the functional approach. These two approaches were undertaken simultaneously and led to very different designs.

The anatomic approach was based on preservation of the cruciate ligaments and soft tissue constraints with replacement or resurfacing of the articular surface. The Gunston polycentric knee (Gunston 1971) was an example of an anatomical knee, as was the UCI knee (Evanski et al. 1976), but with more constrained implants,

replicating the femoral condyles and tibial plateau using casting techniques.

In the case of the Gunston polycentric knee arthroplasty, it was designed to simulate opposing joint surfaces by separate implants for each joint surface. Collateral and cruciate ligaments were both retained to maintain joint stability. The polycentric knee reported to provide significant relief of pain in 86% of 500 knees and the independence and activity levels of the patients increased dramatically (Bryan et al. 1973). It was used predominantly in rheumatoid arthritis and was prone to failure because the patellofemoral joint was not addressed and dislocation and subluxations were common as consequence of ligamentous laxity in the presence of unbalanced soft tissues. Loosening of the tibial components was another problem (Jones et al. 1981; Lewallen et al. 1984). The stumbling block with these anatomical designs at the time, were that these complex geometries were difficult to manufacture, the surgery was technically demanding, and deformity correction was not always possible without extensive soft tissue resection.

The alternative to the anatomical approach was the functional approach, whereby the mechanics of the knee were simplified by resection of the condyles and the cruciate ligaments so the implant could be seated on a flat cancellous bone surface. The concept of the mechanical axis used in osteotomies was used as a guide for implanting the prostheses. Freeman and Swanson were the first to approach condylar total knee design from a predominantly functional perspective. They began their work on the first cemented condylar total knee between 1966 and 1968.

Freeman stated in his implant design objectives (Freeman et al. 1973), that the prosthetic component should be fitted to the bone by a means that spreads the load over the largest possible area of the bone prosthesis interface. Instruments were designed to assist alignment and for checking the balance of the knee. Functional knee replacements ignored the natural obliquity of the joint (the lateral distal femoral angle and medial proximal tibial angle (Figure 2.2)) in favour of a flat surface for the implant to sit on (Figure 2.3).

Success in knee arthroplasty has long been measured by the survivorship of the implant. This was no different in the 1970s and at this stage the functional approach was yielding improved survivorship over the anatomic approach, thus implants such as the Gunston quickly became obsolete.

It has long been accepted that MA in TKA sacrificed the normal kinematics of the knee but this is justifiable because of the mechanical advantage it confers to the implant, and the effect this may have on implant survivorship. Insall back in 1984 stated 'It is our opinion that the objective of prosthetic replacement is to distribute contact stresses across the artificial joint as symmetrically as possible, even if this implies deviation from normal anatomy in general and from individual anatomy in particular' (Scott 2006). Insall went on to predict that an unsatisfactory result from TKA would result if alignment was not correct to within a tolerance of less than 5° of NOA.

Figure 2.2 Lateral Distal Femoral Angle (LDFA) and Medial Proximal Tibial Angle (MPTA), demonstrating the natural joint line obliquity.

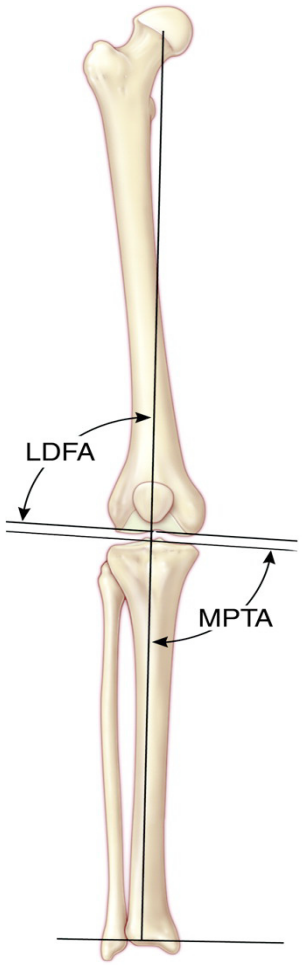
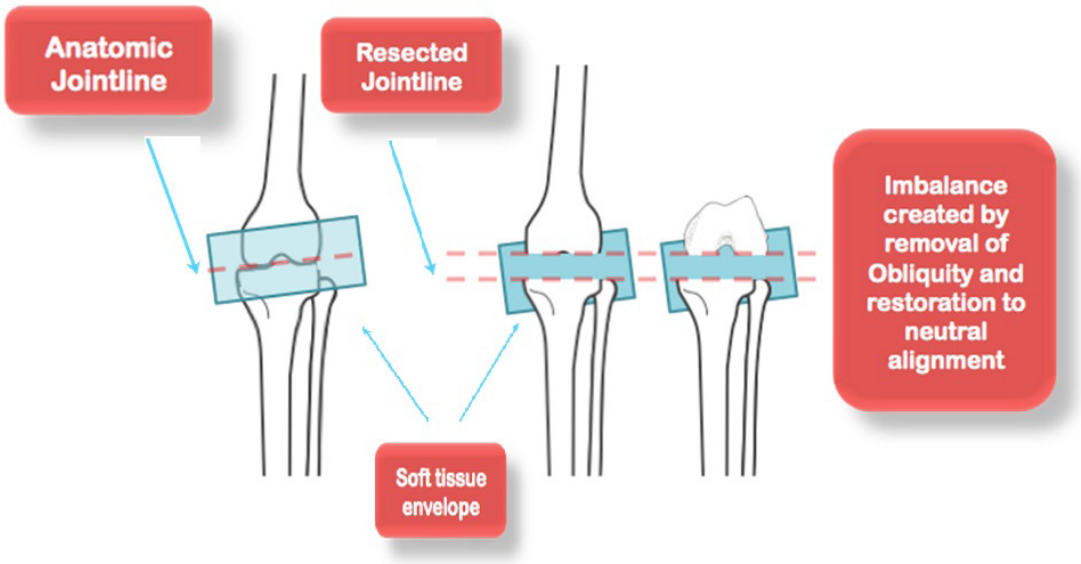


Figure 2.3 Image showing how a cut made perpendicular to the mechanical axis ignores the natural joint line obliquity creating a soft tissue imbalance



2.2 'Thou shalt not varus'- evolution of a concept

The concept of deviation from the mechanical axis representing a degree of varus or valgus malalignment of the knee was becoming established by the end of the 1960s (De Marchin & Maquet 1963). The parameters of what was considered standard alignment were being set. Kettelkamp's early paper on proximal tibial osteotomies reported a tibiofemoral angle of greater than 5° of genu valgus was desirable at improving stance phase flexion and extension (Kettelkamp et al. 1976).

The use of long leg alignment films was popularised by Hagstedt as a way of accurately recreating mechanical alignment in high tibial osteotomies (Hagstedt et al.

1980), utilising the Maquet line from the centre of the femoral head to the centre of the talus (Maquet 1978).

One of the earliest papers that correlated positioning of TKAs to clinical outcome was by Lotke in 1977 (Lotke & Ecker 2006), examining 76 TKAs between 1972 and 1974. Short knee X-rays were compared with a knee evaluation index and found a strong correlation between good positioning of the prosthesis in relation to mechanical alignment and good early clinical results. There was no statistically significant correlation between mechanical failure and X-ray alignment scores.

Important work by Johnson found that when long leg alignment films were taken, if the mechanical axis passed through the centre of the knee the tibiofemoral angle was 5°. The paper also noted that a mechanical axis in the centre of the knee did not confer even distribution of load across the knee but produced greater load in the medial compartment (Johnson et al. 1980).

One of first large series (level IV evidence) comparing alignment and outcome in the same type of knee implant was by Hood in 1981 (Hood et al. 1981), measuring tibiofemoral angles on short leg films before and after 225 Insall-Burnstein knee replacements (tibiofemoral valgus of 7° +/- 5° were deemed satisfactory). Of the three failures none were outside the arbitrary limits that Hood had chosen.

In 1983 Bargren performed a biomechanical study to assess the impact of eccentric loading on tibial component failure using the Freeman Swanson implant. The clinical

outcome with relation to alignment in patients with the same implant using the small area tibial component between 1971 and 1975 was also reviewed (Bargren et al. 1983). 1-13°of tibiofemoral valgus was deemed satisfactory. 91% of the varus knees failed, 100% of the neutral knees failed and 11% of the valgus knees failed. This demonstrates how poor some of the early results with TKA were and malalignment was clearly not the universal cause of failure.

Tew picked up the subject again in 1985, pointing out that although the relationship between alignment and failure may have seemed too obvious to need substantiating, there was little evidence to support it (Tew & Waugh 1985). His paper reviewed 428 TKAs of six different designs between 1972 and 1983 and found that those in extremes of varus and valgus did have significantly higher failure rates. Taking for example, the Manchester knee, 67% of outlier knees failed compared to 43% well aligned knees. Startlingly high numbers by today's standards but it does demonstrate a predisposition for grossly malaligned TKAs to fail.

Our understanding of what constitutes normal alignment was enhanced in 1987 when Moreland et al (Moreland et al. 1987) investigated long leg alignment in normal male adults. The results showed that the overall MA for normal knees ranged from 6.5° varus to 3° valgus. This translated to between 5.8°- 6.0° valgus tibiofemoral anatomical angle.

By 1991 Jeffrey et al (Jeffery et al. 1991) published a series of 115 Denham knees implanted between 1976 and 1981 with at least 8 years of follow up. This study was

well constructed and long leg alignment views were obtained both pre- and post-operatively. This paper offers fairly compelling evidence that malalignment was associated with early loosening. The mechanical alignment of 68% of post-operative X-rays ran through the middle third of the knee, 3% of which went on to loosen. 24% of the remaining knees whose alignment was outside the middle third went on to loosen ($p=0.001$). The results were at variance with those of Smith who found no difference in failure rate in relation to alignment in the Insall-Burnstein prosthesis implanted from 1982-1984 (Smith et al. 1989). At this stage implant design appeared to be having a greater influence on survivorship than alignment.

In 1994 Ritter produced another paper which is commonly quoted as evidence for 'thou shalt not varus' (Ritter et al. 1994). This paper examined alignment on 421 Posterior Cruciate Condylar (Howmedica) TKAs implanted between 1975 and 1983. A criticism of the paper is that alignment values were worked out on short knee films. Out of the eight failures, five were in the varus group, three were in the normal group and none were in the valgus group, based on a neutral tibiofemoral angle of 5-8° valgus. Five out of the eight failures were in patients with either rheumatoid arthritis or osteonecrosis.

In 1999 a correlation between alignment and wear was published by Matsuda (Miura et al. 1999). Twenty MGI knees were implanted between 1988 and 1990 and of the 17 implanted in slight varus, they became more varus overtime with evidence of thinning of the UHMWPE medially. A tibial retrieval analysis of 89 Depuy PFC TKAs implanted between 1984-1998 by Collier found shelf age of the polyethylene,

patient age and varus alignment of greater than 5° all independently contributed to increased medial polyethylene wear (Collier et al. 2007).

By the end of the 1990s TKAs were achieving better patient satisfaction, improved function and >90% implant survival at 15 years (Baker et al. 2007). In the past failure had largely been attributed to complications due to ultrahigh molecular weight polyethylene (UHMWPE). The development of crosslinking UHMWPE was shown to reduce wear rates in the hip (McKellop et al. 1999) and was now being translated to the knee (Pinskerova et al. 2000; Muratoglu 2004).

In 2002 more biomechanical evidence was provided to the argument that varus tibial alignment led to increased posteromedial tibial surface strain in cadaveric and knee simulator studies (Green et al. 2002). The clinical manifestation of this process leading to medial bone collapse was hypothesised by Keating et al (Keating et al. 2002), although not demonstrated in pathological studies. Berend's paper in 2004 (Berend et al. 2004) showed that of 3152 AGC knee replacements implanted from 1983-2000 (incorporating four generations of the AGC) there were 41 tibial revisions, significantly 20 of which were due to medial bone collapse. X-ray analysis of alignment was carried out on short knee films. UHMWPE did not appear to contribute to the failures, although the study incorporated four different sterilisation methods for the PE. This contradicts other studies that have found UHMWPE as the leading cause of failure in TKA (Kettelkamp et al. 1976; Kilgus et al. 1991; Tsao et al. 1993; Feng et al. 1994).

Manual intra- and extra- medullary alignment rods had been used as the standard method of guiding the surgeon in trying to achieve MA. There have been innovations though into techniques to reproduce more accurately MA. Computer navigation (CN) was one such innovation (Brin et al. 2010). As a consequence of CN there was an increase in research comparing alignment results with survivorship using the new technology. The evidence continued to be conflicting. Morgan in 2007 published a series of 197 Kinemax knees implanted from 1990-1993 with a mean 9 year follow-up and was unable to demonstrate any difference in revision rates between alignment groups (Morgan et al. 2008).

Following his article in 1994, Ritter published results in 2009 (Fang et al. 2009) to re-establish the importance of mechanical alignment, this was a continuation of the work by Berend (Berend et al. 2004). This study used multiple different versions of the AGC and 6070 implants from 1983-2006. Critically short knee X-rays were used and measurements were made with a hand held goniometer. The measurement error was not documented. There was a higher failure rate in TKAs when the prosthesis deviated from neutral alignment of 2.4°-7.2° tibiofemoral valgus. Like Berend (predominately because it was the same cohort of patients) varus failure was mostly due to medial tibial collapse.

Ritter's work was in response to research published by Parratte (Parratte et al. 2010). Parratte analysed 398 knee implants between 1985-1990 with long leg alignment films and 15 year follow up. The results showed there was no difference in revision

rate between prostheses implanted in neutral (mechanical alignment 0+/-3°) than those outwith 3° of neutral.

Importantly recent research has also suggested that there does not appear to be a correlation between malalignment and clinical outcome following TKA (Matziolis et al. 2010).

The last publication to date further adds to the ambiguity of the subject. Bonner analysed a total of 501 TKAs divided into an aligned group with a neutral mechanical axis (± 3°) and a malaligned group where the mechanical axis deviated from neutral by > 3°. At 15 years follow-up there was no significant difference in revision for aseptic loosening between the two groups (Bonner et al. 2011). Overall the quality of the literature related to alignment and outcome is confined to historical level IV case series. The most recent publications would suggest that alignment has no impact on implant survivorship.

2.3 Measuring alignment on short vs. long leg X-rays

The accuracy of the radiographs is of paramount importance when considering all the evidence surrounding alignment. Inaccuracy can occur if the X-ray is not centred on

the knee and if there is tibial or femoral bowing, fixed flexion deformity or rotation (Freeman et al. 1973; Jiang & Insall 1989).

The early work on radiographic measurement of mechanical axis was carried out by Moreland (Moreland et al. 1987). His method for measuring mechanical and anatomical axis is still used today. He concluded that if the anatomic axis of the femur is referenced from the centre of the femoral shaft then it does not exit the distal end of the femur at the middle of the knee, so in order to measure the anatomical axis of the femur the angle must be measured before the femoral metaphysis. Sharma modified the method of measuring mechanical axis by measuring from the centre of the femoral head to the femoral notch for the femur and from the centre of the tibial spine to the centre of the talus for the tibia (Sharma et al. 2001).

Hinman's study (Hinman et al. 2006) demonstrated that there is a r=0.88 correlation between the Sharma method of measuring the mechanical axis and the Moreland method of measuring the anatomical axis on long leg films. Correlations (r) between the tibiofemoral angle from short knee radiographs and the mechanical axis angle obtained from full-limb radiographs have been investigated and range from 0.65 to 0.88 (Lotke & Ecker 2006; Issa et al. 2007; Kraus et al. 2005; Hinman et al. 2006; Sheehy et al. 2011). From the studies available it can be concluded that whilst short views will give an indication of alignment they cannot be used to define it accurately.

With this in mind one can be critical of the alignment studies that have used only short knee films. Interestingly Fang's paper on coronal alignment (Fang et al. 2009) referenced work by Peterson as evidence that there was no significant difference between measurements of long and short leg films but Peterson's paper demonstrated a discrepancy of 1.4° with a standard deviation of 2.2°. This could translate to underestimating the tibiofemoral valgus by 5.8° or overestimating it by 3°(Hood et al. 1981; Petersen & Engh 1988). Fang's study also referenced McGrory's (McGrory et al. 2002) paper as demonstrating no difference in long and short films but in fact this paper demonstrated no difference in surgical outcome depending on pre-operative film choice, which is quite different. The relevance of this, is that papers that have only used short leg radiographs, are not accurate when measuring overall alignment.

Hirschmann's paper (Hirschmann et al. 2011) comparing radiographic, 2D CT and 3D CT, as methods for determining the rotational, sagittal and coronal orientation of components, found only low or moderate correlation coefficients for all radiographic measurements except sagittal tibial slope. Three dimensional reconstruction CT is now recognised as the most accurate way measuring alignment.

The literature on alignment and implant survivorship encompasses a huge diversity and evolution of implant and polyethylene designs over the last 40 years. There is large variation in study methodology and analysis. Implants fail for a variety of reasons and having reviewed the modern literature it would suggest that coronal alignment alone is not a good discriminator of implant longevity.

Belleman's recent work confirms the concept of constitutional varus. 'An important fraction of the normal population has a natural alignment at the end of growth of 3° varus or more. Restoration of mechanical alignment to neutral in these cases may not be desirable and would be unnatural for them'(Bellemans et al. 2012).

As survivorship has continued to improve, attention is being turned to reproducing the normal kinematics of the knee. The theory of the epicondylar axis representing the flexion-extension axis has been modified by the work of Eckhoff (Eckhoff et al. 2007). There is a single flexion-extension axis about the distal femur bisecting the femoral condyles but it does not correspond exactly to that of the epicondylar axis. This may have an effect on altering wear patterns when the knee is in motion.

Further work on knee kinematics has demonstrated that there are three axes about the knee where motion occurs and there is a direct relationship between them: The primary femoral axis about which the tibia flexes and extends; a second axis about which the patella flexes and extends that lies proximal and anterior to the primary femoral axis; and a third internal-external rotation axis, in the tibia, that is oriented perpendicular to both the primary and the secondary femoral axis (Coughlin et al. 2003).

The historical concept of mechanical alignment for optimal implant placement needs to be re-examined. Patient dissatisfaction following TKAs ranges from 11-19% (Bourne et al. 2010; Baker et al. 2007). Efforts to improve patient satisfaction by addressing knee kinematics have reignited the debate with regards to implant survivorship and alignment. When implant designs were in their infancy malalignment did appear to predispose to early failure. More recent studies with modern implant designs have not clearly demonstrated this and to make the assumption that misalignment leads to failure would be ignoring a large body of evidence.

2.4 Patient Specific Instrumentation

The increasing use of more detailed imaging and computer software means it is now possible to look at alignment critically in three-dimensions. This is the foundation for PSI. CT and MRI scanning have enabled detailed three-dimensional pre- and post-operative assessment of the knee joint. PSI offers the opportunity to quantify alignment accurately in every plane for the individual patient, and the cutting guides not only set the appropriate coronal orientation, but also the depth of resection, rotation, slope and flexion and extension axis based on the pre-operative template.

A number of orthopaedic device companies have developed some form of patient-specific templating system for TKA. There are variations in the type of image

modality used, software, cutting block and alignment philosophies.

Pre-operative imaging in Patient Specific Instrumentation

All the manufacturers of PSI use pre-operative imaging of CT or MRI to help produce the cutting blocks that are specific to the patient. From these images software packages have been devised to work out alignment and map detailed morphology of the knee so that customised cutting blocks can be produced.

Most companies use a similar technique for MRI scans. The MRI of the arthritic knee is obtained using a high field scanner, 1.5 Tesla or greater. CT is an alternative to MRI. CT can be performed to obtain sagittal images from reconstructed axial images. Protocols vary but some companies perform an isolated CT and use bone as the landmark reference for the PSI, other companies use a CT arthrogram with a bone contrast agent to capture the surface of the articulating cartilage. A consistent pixel size is used. The patient has to be still during the scan to prevent artifact. Slice thickness varies depending on the company.

MRI has the disadvantage that it cannot be used in patients with metal hardware or pacemakers, but it does not have the radiation exposure risks associated with CT scanning. Image acquisition is more time consuming for MRI than CT and movement artifacts are far more likely as a result, although this can still be problematic with CT. For high-resolution images in the region of interest, it is

necessary to use a surface coil with MRI, resulting in three separate scans of the hip, knee and ankle respectively. With CT, high-resolution images can be obtained for the entire limb in one scan (White et al. 2008).

Early research comparing CT and MRI on ovine knees for the use in PSI, demonstrated that bone models generated from MRI scans were dimensionally less accurate and visibly inferior to those generated from CT scans (White et al. 2008). There is no current literature indicating that one modality has superiority over the other.

Computer Software for 3D reconstruction and pre-operative plans

Once the pre-operative CT or MRI scans has been performed, the scans are saved and sent to the company's engineering team for the 3D reconstructions and production of the cutting blocks. Variations exist in the type of software that is used. For the design of PSI, software is used that allows the use of Computer Aided Design (CAD) tools directly on sterolithography (STL) files, known as digital CAD. The software company engineers use programs to place consistent landmarks on the 2D reconstructions and on 3D models. Three dimensional digital models are then created of the femur and tibia and used to determine the optimal implant size. Implant position is determined with respect to alignment in the coronal, sagittal and axial planes, as well as the femoral component matched to the tibial in rotation, with the joint line at the appropriate level and the patella tracking in the correct plane.

Software engineers are responsible for decisions made with regard to anatomical landmarks and optimum implant positioning. Trust is therefore placed in the hands of these trained technicians and it is the responsibility of the companies to ensure accurate and tight protocols are adhered to. A pre-operative plan is created by the software engineers, which can be viewed on the company's website by the operating surgeon. The surgeon has the ability at this stage to review the proposal and make alterations, as they feel appropriate. The surgeon then confirms they are satisfied with the proposal and the company will proceed to the production of the PSI.

Types of Patient Specific instrumentation

Designs differ but the majority PSI either provide the surgeon with entire cutting blocks or drill guides providing orientation for the standard cutting guides for a particular implant. The different manufacturers have specific protocols with regards to removal of osteophytes that have to be adhered to, to ensure conformity of the guides to the patient's anatomy.

Biomet and Zimmer produce PSI that provide the surgeon with drill guides to stipulate the optimum position for the standard cutting guides. The advantage is that the alignment is dictated by the PSI but the surgeon is then using familiar equipment for the rest of the procedure and can double check the cuts with their traditional technique should there be any concerns.

Depuy, Medacta, Stryker and Smith & Nephew provide cutting blocks that dictate the alignment of the distal femoral and proximal tibial cut. These are made from plastic, but in the case of Depuy, the cutting slots are metal lined. Wright Medical design differs slightly in that they embed their standard metal guide into the rapid-manufactured guide, so that the cuts are made through the metal slot of the standard guide.

The majority of PSI manufacturers produce the guides to create neutral mechanical lower limb alignment. The ConforMIS iTotal system is designed to cut the femur and tibia perpendicular to the mechanical axis but then aims to recreate the natural joint line by building in obliquity if necessary to both the tibial polyethylene and condlyes of the femoral implant. ConforMIS is unique in that their system includes not only a patient specific template but also a patient specific total knee implant that is custom built to fit the patient.

The Stryker ShapeMatch® knee differs from the mechanical alignment philosophy and the cutting guides are designed to place the patient's knee into KA, recreate the alignment of the patient's limb in their pre-arthritic state. This is based on evidence that demonstrates considerable variation in the alignment of the normal knee in the general population and that the normal population is not centred around a Hip Knee Ankle (HKA) angle of 0° (Bellemans et al. 2012).

One of the critical differences in the alignment of the ShapeMatch® PSI is that the

Flexion and Extension Axis (FEA) differs from the conventional FEA. Traditionally the FEA is based around a line joining the medial and lateral femoral epicondyles, known as the trans-epidondylar axis. Instead the FEA being used with the ShapeMatch® system is based on a trans-cylindrical axis derived from the sagittal MRI/CT images. The concept of the trans-cylindrical axis has been the evolution of research that first demonstrated that flexion and extension occur about a fixed axis in the posterior condyles (Hollister et al. 1993) and that the posterior femoral condyles are circular in shape (Asano et al. 2001). Eckohoff (Eckhoff et al. 2007) took this concept forward by proposing that this fixed FEA is best approximated by the axis of cylinders fitted to the circular posterior femoral condyles (Fig. 2.4)

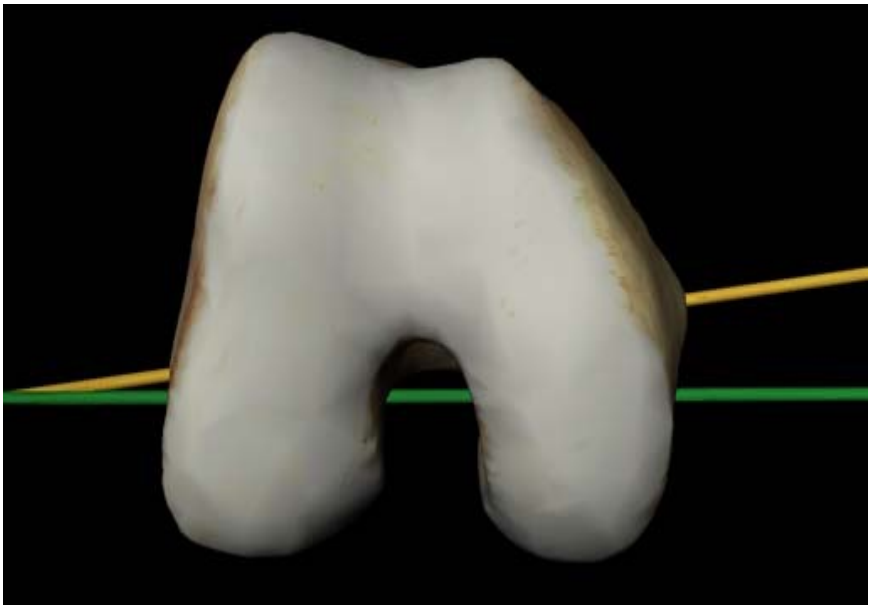
Figure 2.4 A cylinder is superimposed onto the femoral condyle to define a single flexion and extension axis. Reprinted with permission by JBJS (Am)

Eckhoff demonstrated that the trans-cylindrical axis differs significantly from the trans-epicondylar axis. In his study Eckhoff found that the trans-epicondylar axis was proximal and anterior to the FEA with an average difference of 4.6° ± 1.6° (range, 1.8° to 11.3°) (Eckhoff et al. 2007). This axis difference is illustrated in Fig. 2.5.

Figure 2.5-A 2.5-B and 2.5-C. Three-dimensional knee model reconstruction, illustrating the difference between the epicondylar (yellow) and cyclindrical (green) axes. Fig 2.5 A Medial (left) and lateral (right) views.

Figure 2.5-B Coronal view with cylindrical axis.

Figure 2.5-C Transverse view with cylindrical axis.



The alteration in FEA to the trans-cylindrical axis is significant, as relative to the traditional trans-epicondylar axis the femoral component is implanted in a position of internal rotation, and this will in turn have an impact on the kinematics of the patella femoral joint.

The PSI guides aiming to create neutral mechanical lower limb alignment has again produced a raft of research assessing their accuracy. Two Level I RCTs (Chareancholvanich & Narkbunnam 2013; Hamilton & Parks 2014) have demonstrated no discernable difference in mechanical alignment with the use of PSI and a smaller RCT suggested a slight improvement in alignment accuracy in comparison to conventional guides (Noble et al. 2012). The evidence is ambiguous as to whether PSI has improved the rotation alignment in TKA. Silva et al (Silva et al. 2013) suggested that the rate of tibial component internal rotation was reduced with PSI and Vundelinckx (Vundelinckx et al. 2013) found PSI to reproduce the tibial slope, with great accuracy. Parratte (Parratte et al. 2013) was unable to demonstrate improved component rotation. What appears to be the case though is that PSI is certainly no worse that manual instrumentation methods.

Much like computer navigation some research has focused on whether PSI has translated into improved clinical results after TKA when compared with conventional methods. There have only been a couple of studies that have looked into this. One study of Level III evidence (Yaffe et al. 2013) did demonstrate that

PSI was associated with a statistically significant improvement in Knee Society Functional score at 6 month post-TKA as compared to manual TKA. However the patients were not well matched at base line, the PSI group did have higher pre-operative scores therefore limiting the ability to draw definitive conclusions from the post-operative scores. These small improvements may be attributable to improvements in component rotation and positioning or improved component size accuracy when compared to manual alignment techniques. The only other published trial looking at functional outcome in 31 patients, operated on with the Visionaire PSI, compared to an equivalent control group with manual instrumentation, found no statistical significant difference in post-operative pain, satisfaction, functional outcome, hospital stay, blood loss, radiographical alignment and precision of bone cuts between the two groups (Vundelinckx et al. 2013). In these studies the aim of the PSI cutting blocks was to reproduce neutral mechanical alignment. Given that this is a deviation from the knees' normal anatomy anyway this would support the null hypothesis that deviation from neutral mechanical alignment does not affect functional outcome.

Another theoretical attraction of the PSI is that it can save time in the operating theatre as the application of the cutting blocks to the bone is quicker than making manual adjustments with intra- and extra- medullary instrumentation. This appears to have been born out by some of the literature (Chareancholvanich & Narkbunnam 2013; Boonen et al. 2012). As pre-operative plans have pre-determined the size of the implants there is an improvement in cost and efficiency of the number of surgical

trays that need to be opened and a reduction in implant inventory held at the hospital (Nunley et al. 2011).

2.5 Kinematic alignment studies

Kinematic alignment as a concept was beginning to be investigated towards the end of the last decade. OtisMed® (Almeda, CA, a subsidiary of Stryker Orthopaedics, Mahwah, NJ, USA) had developed software to 3D map the knee using CT images to reconstruct the joint in its pre-arthritic state. It was Stephen Howell, MD, a co-founder of OtisMed® who was first to publish on 48 custom-fit knees using the Vanguard Knee (Biomet, Inc) (Howell 2008) reporting that his case-controlled study did not detect any adverse effects or long-leg malalignment that would preclude the use of the custom-fit technique. This was a pilot study and the aim was to recreate natural pre-arthritic alignment of the knee with the cutting blocks.

This was soon followed by a publication by Dr Hozack, who was then the assistant chief editor of the Journal of Arthroplasty. This may have contributed to his small case series (Level IV evidence) being published in his journal. The case series of four OtisKnee™ cutting blocks were used to produce kinematic alignment followed by implantation with the Stryker Triathlon component (Klatt et al. 2008). Computer navigation was used intra-operatively to assess what the patient's natural alignment would be. Two patients were outliers with predicted alignment greater than the

perceived safe zone of 3°. The paper concluded that kinematic alignment was not a safe technique. After the pilot study, Dr Hozak declined to evaluate further the OtisKnee™. This paper was met with a strongly worded response by Howell who felt that jettisoning the whole concept on a case series of four was unjust and that his personal experience of 700 OtisKnee™ operations did not reflect Hozack's concern (Vernace & Bodenstab 2008). In fact Howell went on to publish his cohort of 198 KA patients and demonstrated no catastrophic implant failures with a minimum of 31 months follow up (Howell et al. 2012).

Early research on cadaveric knees did appear to demonstrate that the KA PSI cutting blocks were reproducing satisfactory alignment correlating to the pre-operative plan (Nogler et al. 2012). A case series testing specifically the intra-operative reliability of ShapeMatch® cutting guide placement concluded that the technique was accurate (Clark et al. 2013). The study was well constructed with the accuracy of the cutting blocks tested with CN. The operating surgeons were blinded to the CN display results.

The first published RCT comparing KA and MA was by Dossett (Dossett et al. 2012) and demonstrated improved outcome in the WOMAC and Oxford Knee Score at 6 months in the KA group. It should be observed that the paper was published in 'Orthopedics', which is a journal that charges a fee for submission of articles. The study was randomised but did have a high patient withdrawal rate, with 32 of the 120 patients initially recruited not undergoing surgery. The 2 year results were then

published in 2014 (Dossett et al. 2014). These again demonstrated superior WOMAC and Oxford Knee Scores in the KA group. Using the Effective Public Health Practice Project quality assessment tool for quantitative studies the Dossett paper provides moderate evidence due to rate of patient withdrawal. The author did not respond to my numerous requests to review the raw data from the study, for the purposes of a meta-analysis on the subject.

Vanlommel published a study that suggested post-operative mild varus alignment is in fact associated with improved functional outcomes (Vanlommel et al. 2013). After follow-up of 5–9 years in a research population of patients with pre-operative medial arthritis and varus alignment of the knee, those with post-operative mild varus alignment were shown to have better clinical results in comparison to patients corrected to neutral or left in severe varus. The study reviewed WOMAC and Knee Society Scores retrospectively. It should be noted that whilst the mild varus group (9.3° +/- 3.7°) had improved outcomes, the group left in severe varus did worse than the neutral group. The study therefore suggested that under correction might be associated with better outcomes when compared with restoration to neutral, but only in a selective cohort with mild varus (Level III evidence).

Howell has published the 6 year follow-up on his initial cohort of KA TKA and did not reveal a higher than average failure rate (Howell et al. 2013). At a mean of 6.3 years (range, 5.8–7.2), implant survivorship was 97.5% and revision-rate per 100 component years 0.40. Three implants had been revised (one deep infection, one

loose tibial component and one patella instability); two loose patella components were pending revision and considered failures. This failure rate is in keeping with the 5 year risk of revision for cemented implanted quoted in the NJR (NJR 2017).

A knee kinematics computer simulation study (Ishikawa et al. 2015) has suggested that by restoring the natural joint line of the knee, greater femoral rollback and more external rotation of the femoral component is achieved with KA TKA than with MA TKA, producing more normal knee motion. However, patellofemoral and tibiofemoral contact stresses were increased in the KA TKA, raising theoretical concerns over implant survivorship and the possibility of increased anterior knee pain. A small study looking at muscle activation with electromyography and function has also favored KA over MA (Belvedere et al. 2015), the sample size for this was small (17 patients), so results should be interpreted with caution.

A recent publication on the subject of KA was an independent RCT comparing KA with MA, producing Level II evidence (Calliess et al. 2016). Age and sex data was not available but the primary outcome measures of the WOMAC and Knee Society Score were both superior in the KA group. The study did however demonstrate that more outliers with poor outcomes were also seen in the KA group.

Since the initial draft of this thesis, a further RCT has been published that did not demonstrate any improvement in the Oxford knee Score, WOMAC, and the

Forgotten Joint Score at 2 years when comparing MA and KA. This was a double-blinded study with 95 patients in total and no patients were lost to follow-up (Young et al. 2016).

In conclusion the early literature on kinematic alignment should be interpreted with some caution. The largest body of work is from Stephen Howell (Howell et al. 2013; Howell et al. 2012; Howell et al_2013), who has a vested interest in the technique. The results of functional outcome in patients who have received KA TKA from the small number of studies performed so far have been mixed. Certainly more research is required before any definitive conclusions can be drawn on the efficacy of the technique.

2.6 Patient outcomes from Total Knee Arthroplasty

Measurement of patient outcome following TKA

TKA is now a more common procedure than total hip arthroplasty but patient satisfaction following TKA surgery remains inferior (Miura et al. 1999; Bourne et al. 2010; Wylde et al. 2009; Baker et al. 2007). When we refer to patient satisfaction it is important to understand exactly how and what has been measured. Accurate outcome assessment is a fundamental aspect of orthopaedic research. It is essential when interpreting data that the benefits and limitations of the outcome instruments

are fully understood.

In the long term the success of an orthopaedic procedure is often quantified by the time until revision surgery is required, depicted in survival curves, and forms the basis of a large part of the joint registry data (NJR 2017). Revision has been regarded as the definitive outcome measurement for survival analysis of orthopaedic implants. Survivorship rates of implants are now very good but without knowledge of the reason for the revision surgery results can be misinterpreted. Price et al (Price et al. 2010) have argued that survival based on revision alone provides an inaccurate impression of outcome in younger TKA patients and a better representation of the success of TKA should include pain and function as endpoints.

In the short term we can measure pain and function as endpoints using a variety of objective or subjective tools. Objective data tends to be measured and collected by health care professionals, it often involves measurement of the patient's ability to perform functional tasks and interpretation of clinical and laboratory based tests. Subjective outcome measures include patient reported outcome measure (PROM) questionnaires, asking the patient to report on the perceived health status. In order to interpret outcome measures with confidence it is essential that the outcome tool has been developed using appropriate methodology and has had published evidence of satisfactory psychometric properties such as acceptable levels of reliability, validity and sensitivity (McKellop et al. 1999; Beard et al. 2010).

There are limitations with all forms of outcome measures. Objective measures judged exclusively on the basis of empirical assessment of quantitative or technical variables are prone to bias, as objective success of an intervention does not necessarily reflect the improvement in patient's quality of life, and does not necessarily take into account the patient's pain (Jackowski & Guyatt 2003).

PROMs provide the patient's perception of their health and may not truly reflect what they are capable of from a functional perspective. A self-reported outcome questionnaire together with a rating of the patient's satisfaction with the outcome, is however valuable information about the success of any intervention (Jackowski & Guyatt 2003), and provides insight into what extent the patient feels the intervention has been a success (Timmins 2008). PROMs can be divided into generic, disease specific and joint specific instruments. Generic quality of life instruments are suitable for a broad range of patient groups across the general population whereas disease specific outcome instruments assess the quality of life of a patient who is suffering from a specific disease or health condition. Disease specific outcome instruments generally have higher sensitivity than generic 'quality of life' instruments but they often lack the ability to detect unforeseen effects of a health intervention (Garratt et al. 2001). PROMs are now widely advocated for data collection following TKA (Bream et al. 2010; Beard et al. 2010; Price et al. 2010; Bream & Black 2009) and are in fact now a requirement of NHS patients undergoing TKA. From April 2009 the EQ5D and Oxford Knee Score have been collected nationally in England for all patients undergoing a TKA, although this is not the

same in Scotland. It is acknowledged that no one tool is superior when assessing outcome (Davies 2002). Validity, reliability, responsiveness, interpretability and the floor and ceiling effect can all effect patient outcome measures alike (Beard et al. 2010) so although time consuming, using a combination of outcome tools is likely to give the most reliable assessment of the true success of the surgery. In Chapter 6, the RCT, generic as well as joint specific outcome measures were used, as well as a number of function tests. The literature regarding these specific tests is discussed below.

Short Form (SF)- 36 health and quality of life scores

It is recommended that a generic instrument should be used together with a condition-specific one (Dieppe 1995). The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (McHorney et al. 1994) is designed to measure general health status. It consists of 36 questions with Likert-box response options. Questions are grouped into eight domains with scores ranging from 0 (poor health) to 100 (good health). The SF-36 has been shown to have good psychometric properties and is applicable to patients suffering from a wide range of health conditions. The SF-36 has demonstrated good overall ratings in patients with OA of the knee (Veenhof et al. 2006; Garratt et al. 2004). Together with the use of WOMAC/KOOS, the SF-36 is the most recommended and commonly used outcome tool for evaluating pain and function in patients with knee OA.

EuroQol-Five Dimensions (EQ-5D)

EQ-5D measures health-related quality of life by assessing five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with three levels of severity (some problems, moderate problems, extreme problems) and has a visual analogue scale (VAS) which allows individuals to rate their own health state on the day of the assessment ranging from 0 (worst imaginable state) to 100 (best imaginable state) (EuroQol Group 1990). The EQ-5D has been validated in population studies (Shafie et al. 2011).

The University of California at Los Angeles activity score (UCLA)

The UCLA scale is a simple scale ranging from 1 to 10. The patient indicates their most appropriate activity level, with 1 defined as 'no physical activity, dependent on others' and 10 defined as 'regular participation in impact sports'. The UCLA scale has been criterion-validated examining the correlations between UCLA scores and objective measures of physical activity obtained with pedometers (Zahiri et al. 1998). In comparison to other PROMs relating to physical activity the UCLA scale has been demonstrated to be reliable, feasible, and a valid instrument for assessment of activity levels in patients undergoing TKA (Naal et al. 2009).

The University of California at Los Angles activity score (KOOS)

The Knee Injury and Osteoarthritis Outcome Score (KOOS) includes and expands on the WOMAC score and assesses five dimensions in 42 questions (pain, symptoms, function in daily living (ADL), function in sports and recreation (Sport/Rec), and in knee related quality of life) (Roos et al. 1998). Results are not combined in a single score, but presented as five different values representing five dimensions of the instrument. The KOOS has good evidence of reliability, validity and responsiveness, and has been recommended as a good choice for long and short term assessment of knee OA, anterior cruciate ligament (ACL) reconstruction and meniscus injury (Veenhof et al. 2006; Roos et al. 1998).

The American Knee Society Score (AKSS)

The American Knee Society Score was evolved from the Hospital for Special Surgery system and is divided into two distinct parts. The first is a Knee Score out of 100, and the second a Functional Score also out of 100. It was developed in this way so that the Knee Score would be independent of function and therefore not subject to deterioration due to co-morbidity. The Knee Score component measures, pain (out of 50), range of motion (out of 25), stability (out of 25) with antero-posterior and medio-lateral scored separately. Calculations are made for flexion contracture, extension lag and alignment. The maximum score for arc of movement is achieved at 125° of arc. The functional component considers walking, stair climbing and makes

deductions for the use of a stick or crutch. The American Knee Society score is used widely in the UK, and for that reason it was selected for this study. Bach et al (Bach et al. 2002) found that the Knee Score offered only poor inter-observer reproducibility whilst the function score showed good inter-observer reproducibility. This is likely a reflection of accurately measuring alignment to within 3°. The wide variations in inter-observer correlation coefficients need to therefore be considered when interpreting the results from the AKSS.

Timed up and go (TUG)

This is a simple test of patient mobility, where by the patient is observed and timed while they rise from an armchair, walk 3 metres, turn, walk back, and sit down again. As a functional test it has been validated and demonstrated reliable inter and intra-rater correlation for quantifying functional mobility and following clinical change over time (Podsiadlo & Richardson 1991).

Timed up and down stairs (TUDS)

The Timed up and down stairs tests the patient's ability to ascend and descent a set of stairs. The patient is timed from toe off on one side of the staircase to leading heal strike on the other side of the staircase. The TUDS has been evaluated for reliability and validity and has demonstrated good intra-rater, inter-rater, and test-retest reliability and correlated closely with the TUG test and other clinical measures of functional mobility and balance (Zaino et al. 2004).

Two minute walk test

A 10 metre track is marked out in the physiotherapy gymnasium with cones at each end. The patients were timed for 2 minutes and the distance they covered in that time is measured. The Two minute walk test has been shown to correlate highly with the distance covered during a six minute walk test (Butland et al. 1982; Kosak et al. 2005; Connelly et al. 2009). The test is useful as the results can be compared against norms established by the National Institute of Health (NIH) Toolbox for the Assessment of Neurological and Behavioral Function Norming Project (Bohannon et al. 2015). The Two minute walk test has established consistent intra-class correlation coefficient with good reliability (Bohannon et al. 2015).

Peak Quadriceps and Hamstring Torque

The digital myometer is a tensiometer that can measure the tension in a restraining belt attached to the patient. The tension generated in the belt varies depending on the placement of the belt on the patient's limb, so it is very important that it is set up in a standardised fashion for each patient to reduce intra and inter-operator error. For measurement of the quadriceps' strength the belt is attached to the patient's leg 30 centimeters below the patient's tibial tuberosity ensuring that the patient's leg is flexed to 90° over the side of the bed and hanging freely. For measurement of peak hamstring torque the belt is again attached 30 centimeters distal to the tibial tuberosity. The lever arm and the Myometer reading are recorded and multiplied to obtain the moment about the joint.

Pain assessment

Pain can be assessed using the Numerical Rating Scale (NRS). This is an 11 point scale where the endpoints are the extremes of no pain and pain as bad as it could be. The NRS was graphically delivered with numbers 0-10 enclosed in boxes. The validity of the NRS has been well established (Jensen & Karoly 1992; Korff et al. 2000; Williamson & Hoggart 2005).

Forgotten Knee

The concept of the patient having forgotten they have an artificial joint has gained popularity recently, as the ultimate goal in joint arthroplasty. The FJS-12 Knee was published in 2012 (Behrend et al. 2012). Further studies have gone on to demonstrate good validity and reliability of the forgotten joint score in evaluating the outcome of TKA (Thomsen et al. 2016). The FJS-12 is a 12-question outcome measure, which in its self is time consuming. More recent studies have tried to distill the information into a single question (Eymard et al. 2015). In this study the patients were asked two variations on the theme. Firstly: do you feel like you have forgotten that you have an artificial knee? Yes/No; secondly: are you aware of your artificial joint? Never, almost never, seldom, sometimes and mostly. The aim was to look at the correlation between the two questions to see if a simple yes or no answer is valid.

How successful is TKA?

Having discussed that there are a wide variety of assessment tools available in TKA to measure patient outcome, the success of the procedure can be quantified by what has been measured. As described previously, if using implant survivorship as the outcome measure, TKA is now a successful operation. The overall survivorship of cemented total TKA is now >95% at 9 years as quoted by the National Joint Registry (NJR 2017).

Patient satisfaction is an important outcome measure and this can be measured by the validated, self-administered satisfaction scale (very satisfied, somewhat satisfied, somewhat dissatisfied, very dissatisfied) developed by Mahomed et al (Mahomed et al. 2002), which assesses overall satisfaction as well as that of pain relief and the ability to perform daily and leisure activities. Using this outcome system in a study by Bourne (Bourne et al. 2010), 19% of primary TKA patients were not satisfied with the outcome. Satisfaction with pain relief varied from 72–86% and with function from 70–84% for specific activities of daily living. Expectations not met, poor 1-year WOMAC, pre-operative pain at rest and a post-operative complication were all independent predictors of dissatisfaction. An overall review of the literature reports patient satisfaction ranging from 75-89% following TKA (Anderson et al. 1996; Bourne et al. 2010; Wylde et al. 2009; Heck et al. 1998; Scott et al. 2015).

The primary reason for people electing to undergo TKA is chronic pain (Hawker et

al. 1998). It therefore follows that pain relief should be a key outcome measure. Research in the literature regarding pain indicates that TKA provides good pain relief. Using the WOMAC pain scale, on which a score of 0 represents maximal pain and 100 represents no pain, mean scores improve from 40–45 pre-operatively (Jones et al. 2000; Lingard et al. 2004) to 76 at 6 months (Jones et al. 2000), 82 at 2 years and 88 at 10 years post-operative (Wright et al. 1998).

Functional ability following TKA is more unpredictable than pain relief. When using the functional component of the WOMAC score as an outcome measure it consistently shows lower results than that of pain. The average WOMAC function scores show improvements from 43 pre-operatively (Lingard et al. 2004; Jones et al. 2000) to 70 at 2 years, 78 at 5 years (Bullens et al. 2001) and 79 at 10 years (Wright et al. 1998). Thirty-three percent of patients report no functional limitations with their replaced knee (Wright et al. 1998) and nearly 20% of post-operative patients feel that their operation was not successful in enabling them to resume their regular physical activities (Jones et al. 2000). With regards to functional ability at 2–7 years post-operatively in comparison to their function before surgery, in a study by Jones et al, 11% of patients thought their current function was the same or worse than pre-operatively (Hawker et al. 1998).

In terms of the restrictions experienced when returning to sporting activities post-operatively, it appears the level of restriction from the TKA is related to the demands of the particular sport (Noble et al. 2005) with an overall net decrease in sports

participation post-operatively (Huch et al. 2005).

Effects on outcome

The role of pre-operative status is important in outcome following TKA. The poorest functioning patients pre-operatively make the largest proportional gains, but they retain the lower spectrum of post-operative functional scores. Low pre-operative physical and mental health scores are the strongest determinants of limitation to post-operative function at 1 and 2 years (Lingard et al. 2004).

Pre-operative variables are associated with poorer improvement in post-operative function. A higher chance of 'less functional gain' was reported for patients with a BMI over 40, low mental health scores, increasing age and poor quadriceps strength. The BMI and poor quadriceps strength had the most impact, with more than a 2-1 odds ratio of poor functional gain post-operatively (Franklin et al. 2008).

Socio-demographic, psycho-social and medical factors have all been identified as predictors of poor outcome, but still some unsatisfactory outcomes cannot be explained (Wylde et al. 2007).

Meeting patient expectations is of the utmost importance in achieving patient satisfaction after primary TKA. Several studies have demonstrated this correlation

(Chesworth et al. 2008; Heck et al. 1998; Janse et al. 2004; Mahomed et al. 2002). In addition, certain pre-operative factors (advancing age, living alone, less than 90° flexion and pain at rest) and post-operative factors (a complication requiring hospital readmission and a low 1 year WOMAC) appear to be associated with dissatisfied primary TKA patients (Bourne et al. 2010).

Decisions made by the health care team also impact on outcome. Implant design, surgical technique, knee kinematics, peri-operative complications, and post-operative physiotherapy can all influence patient outcome, although to what extent, is difficult to quantify (Dennis et al. 2007).

2.7 Bone mineral density and Total Knee Arthroplasty

Much of the concern surrounding the concept of kinematic alignment in TKA is the theoretical risk of early implant failure. For the early designs of TKA it was felt that compressive failure of tibial trabecular support was a leading mode of tibial component loosening (Bargren et al. 1978; Cameron & Hunter 1982; Ducheyne et al. 1978). Early survivorship studies demonstrated predominantly tibial collapse in varus implanted components (Hood et al. 1981; Ritter et al. 1994). Although observation of failure can be reported in survivorship studies, bone mineral density measurement is an alternative way of quantifying the effects of altered mechanical loading of the knee joint and the effects of stress shielding around the implant.

Dual Energy X-Ray Absorptiometry (DEXA) was a technique that was developed in the 1970s as a way of measuring Bone Mineral Content (BMC) and Bone Mineral Density (BMD). Initial work was concentrated on the lumbar spine (Roos et al. 1975; Wilson & Madsen 1977; Mazess 1982; Krølner & Ntelsen 2011), and the effect of ageing on bone loss (Riggs et al. 1981). Grading systems were developed for osteoporosis using bone scanning around this time, and there was an acknowledgement of the relevance of examining various parts of the skeleton and their relationship to one another (Dalén & Lamke 1974).

Functional strain was identified as a determinant for bone remodelling (Lanyon 1984) and the relationship of BMD to TKA began being investigated in the 1980s. Early retrospective roentgenographic studies looked at stress relief osteoporosis of the anterior femoral condyles in TKA (H. U. Cameron & G. Cameron 1987) as well as bone loss in the distal anterior femur following TKA (Mintzer et al. 1990).

The first papers looking specifically at bone mineral density around joint replacements involved the hip (Kiratli et al. 1996), demonstrating that localised bone loss can be induced by stress shielding. The concept was first used for the knee by Bohr (Bohr & Lund 1987; Bohr & Schaadt 1987). Bohr initially looked at the distribution of BMD in the proximal tibia in the normal adult population and demonstrated a decrease in BMD with age and that there was greater BMD under the

medial tibial condyle than the lateral. This was in accordance with biomechanical studies of variations in strength and structure of cancellous bone at the knee (Behrens et al. 1974; Goldstein et al. 1983). It was discovered that the most reliable regions to measure BMD in the proximal tibia were just distal to the subchondral plates, where the trabecular structure transfers weight load to cortical bone of the tibial shaft, due to the relatively uniform mineral distribution (Hall 1966).

Bohr (Bohr & Lund 1987) then went on to perform a clinical study in nine patients followed up for 2 years after they had undergone uncemented TKA. The study found that there was an even increase in the BMD under the prosthesis 6 months post-operatively. This was felt to reflect bone remodelling at the bone-prosthesis interface, similar to that of a fracture and then an apparent slow decrease for 2 years, although no details were given on the type of knee pathology or pre-operative deformity and the study design may have resulted in bias by gender related inter-individual variance.

Hvid (Hvid et al. 1988) performed a similar study examining remodelling of the tibial plateau after cemented TKA using CT bone densitometry and examined the relationship of tibiofemoral alignment to BMD. The results differed from Bohr's uncemented study. At the early post-operative measurements there was abnormal mediolateral distributions of density, closely related to the pre-operative tibiofemoral angle, a trend that normalised after 3 months in knees with pre-operative valgus and after 2 years in knees with pre-operative varus. Although the overall change after

knee replacement was loss of density, the less loaded condyle pre-operatively had a slight tendency towards increasing density with time.

Stress shielding around the femoral components was confirmed by Peterson (Petersen et al. 1995) with the use of DEXA, again in uncemented TKA implants, but this study did not address the implant/tibial interface. The same author went on to compare different types of uncemented femoral components and showed that the porous coating of the implant did not appear to make a difference to the overall reduction in BMD around the distal femur (Petersen et al. 1996).

The early studies looking at long-term changes in BMD were yielding differing results. These diverging results may have been caused by several factors, such as the use of different imaging techniques and ways to analyse and present the material, and the use of differing rather small areas under the tibia for the bone density measurements. Validation of a protocol for identifying regions of interest (ROI) around the knee was established by Trevisan (Trevisan et al. 1998), this took into account areas around both the distal femur and proximal tibia. Further validation taking into account the effects of rotation was undertaken by Therbo (Therbo et al. 2003). What seems to be in agreement is that inhibition of bone formation and increased bone reabsorption occur in response to trauma and immobilization leading to a reduction in the bone mass, certainly in the early post-operative period. Soininvaara (Soininvaara et al. 2008) studied bone metabolism around TKA in more detail by examining both BMD and single-photon emission CT with the use of 99m

Tc-methylene disphosphonate in regions of interest around the prosthesis.

Li et al. (Li & Nilsson 2000) were the first to look at both the effects of uncemented and cemented implants and pre-operative alignment on BMD in the proximal tibia following TKA. Their paper reported that the average level of BMD in the proximal tibia temporarily decreased during the initial 3 months and then the baseline level was restored over a 2 year period. They were unable to identify any differences between cemented and uncemented fixation with regards to the post-operative changes in BMD. Interestingly considerable variation was observed on an individual basis and BMD appeared to be closely related to the baseline level, which in turn was related to the magnitude of deformity of the knee before the operation. Knees with varus alignment had higher levels of bone mineral density than those with valgus alignment, a finding echoed in early work (Bohr & Lund 1987; Hvid et al. 1988). The study found that pre-operative varus alignment with loading of the medial side of the knee seemed to be a strong stimulus for bone formation not only in the medial region but also in all parts of the proximal tibia. By re-aligning the varus knees to neutral alignment the pre-operatively existing stimulus for increased bone remodeling on the medial side was removed and a more evenly distributed load at the knee stimulated a loss of bone in knees with high levels of BMD and an increase of bone in knees with low levels. This finding was also noted in a similar study by Soininvaare et al (Soininvaara et al. 2004). The baseline ROI BMD was significantly higher in the varus knees than in the valgus aligned knees and the region under medial tibial plateau decreased in BMD during the follow-up in pre-operatively

varus knee. Correction to neutral mechanical alignment in both varus and valgus knees showed bone remodelling giving similar medial and lateral BMD values. This should come as no surprise as the trabecular bone is effectively following Wolff's law of the bone adapting and remodelling in response to the mechanical stress under which it is placed. These studies have suggested that even distribution of BMD is to the advantage of the implant, but equally there has been no correlation between peri-prosthetic tibial fracture and alignment. Fracture around primary TKA is an uncommon complication with a quoted risk of 0.6% at 5 years (Meek et al. 2011). Tibial loosening is the more common cause of implant failure and it seems plausible that by decreasing the BMD in varus knees, the bone implant interface could also be weakened.

Alignment has been demonstrated to play an important role in BMD both before and after TKA. Much of the literature using DEXA appears to have concentrated on the effects of porous coatings on uncemented implants (Petersen et al. 2005) and cemented versus uncemented implants (Abu-Rajab et al. 2006) on BMD, possibly to justify the use of more expensive implants. In isolation, without alignment statistics, these studies are of less value. There is certainly scope for further research into the effect of alignment on BMD and the potential implications on implant failure. With regards to KA the hypothesis is that by recreating the natural jointl ine obliquity this may lead to alteration in BMD, particularly around the tibial component. For example a varus knee may experience increased BMD under the medial tibial plateau. This is explored in chapter 6.

Chapter 3 Proof of Concept Study Examining Kinematic Alignment in Total Knee Arthroplasty

3.1 Introduction

The purpose of the whole doctorate was to research what impact KA will have on the outcome of TKA. The research involved the introduction of two new technologies, (1) computer software for determining the alignment of the knee in the pre-arthritic state; Otismed® ShapeMatch® technology (Stryker Corporation, Mahwah, NJ, USA, FDA clearance) and (2) Otisknee™ custom cutting guides (Stryker Corporation, Mahwah, NJ, USA, FDA clearance).

The study centre was the first in Europe to use this new technology. As such it was imperative that the new technology was introduced in a responsible manner. The proof of concept study was used to ensure that the new products were safe and that surgical techniques were reproducible. The purpose of the study was firstly to assess the pre-operative plans and examine how the proposed alignment corresponded with accepted alignment parameters. The second purpose of the study was to assess the cutting blocks and see how accurately they recreated the pre-operative plans.

3.2 Methods

An initial single surgeon case series between January 2010 and August 2012 was performed to look at the accuracy of the Otismed® ShapeMatch® cutting blocks.

Twenty-five patients were recruited from the planned operating list of one surgeon (VIM) at the Exeter Knee Reconstruction Unit, Royal Devon and Exeter Hospital. Pre-operative HKA radiographs were performed. Patients were provided with an information booklet regarding the new technology. As this was a case series with an FDA approved device Ethics Committee Approval was not required. All patients who met the inclusion/exclusion criteria listed below were considered for the ShapeMatch® TKA.

Inclusion criteria:

- Age between 18 to 85 years with a diagnosis of degenerative osteoarthritis

Exclusion criteria:

- Varus or valgus deformity $>10^{o}$ from the mechanical axis or a flexion contracture of $> 20^{o}$
- If they had undergone any orthopaedic procedure to the lower limbs within the past year
- A history dissatisfaction following contralateral partial or TKA
- Any implanted prosthesis that would interfere with MRI scans
- A neuromuscular or neurosensory deficiency

- An inflammatory arthropathy

All 25 patients had MRI scans of their arthritic knee performed at the unit, according to the Triathlon® Knee System with the Otismed® ShapeMatch® technology protocol with the aim of producing cutting blocks to assist the surgeons to implant the prosthesis in KA (Stryker Corporation, Mahwah, NJ, USA, FDA clearance). The cohort was representative of the standard patient population.

OtisMed® ShapeMatch® Technology used 3D computer software to determine the position for the custom made cutting blocks (OtisKnee™ custom cutting guides) to be seated intra-operatively on the patient's distal femur and proximal tibia. A Magnetic Resonance Imaging (MRI) scan was used to reconstruct a 3D model of the patient's knee. The aim of the ShapeMatch® software was to restore the arthritic knee back to its pre-arthritic alignment by filling in any cartilage defects in the knee before the sizing and fitting of the cutting blocks took place.

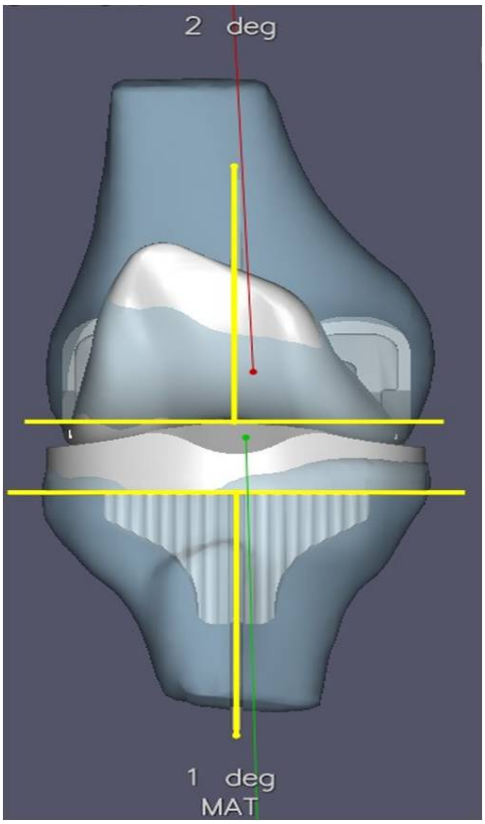
The surgeon used the ShapeMatch® system according to the manufacturer's instructions. The pre-operative MRI of the arthritic knee was obtained using a high field scanner. The pulse sequence consisted of a two-dimensional (2D) sagittal PD sequence with a standard protocol to determine the range for the repetition time [TR] and echo time [TE]. The general scanning parameters included a 16cm field-of-view (FOV) centred at the knee joint, 256 matrix interpolated to 512 resolution and 2mm slice thickness with no gap at the knee. Images were also taken of the femoral head

and distal tibia to determine alignment. If the patient moved during the scan and the radiographer detected artifact, the scan was repeated.

The MRI scans were saved and sent to Stryker's engineering team and 3D reconstructions were made from the sagittal MR slices for the production of the cutting blocks. Filling in the articular defects from each sagittal image generated the normal knee model. Defects of the articular cartilage were identified in the MR images by recognising discontinuity of the usually smooth articular surface. Implant position was determined with respect to alignment in the coronal, sagittal and axial planes, with the aim of creating the alignment of the knee in the pre-arthritic state.

From the normal knee model the sizes of the femoral and tibial components were determined. Matching the posterior condyles of the femoral component to the femur set the femoral rotation, and flexion was referenced from the anterior femoral cortex to ensure no notching. The amount of distal femoral resection was set to 8mm, which is the thickness of the implant. Tibial rotation was determined by aligning the middle aspect of the tibia to the distal aspect of the femur. Tibial slope was determined by matching the posterior cortex of the tibia parallel to the tibial stem. The amount of tibial resection was set to match the width of the implant including the polyethylene, this was 9mm. The surgeon was sent online patient plans for approval before the cutting jigs were created (Figure 3.1).

Figure 3.1 Image showing the pre-operative plan that was sent to the surgeon. In this case proposing 1°of varus on the tibia and 2° of valgus on the femur



Once the surgeon was satisfied with the pre-operative plan the femoral and tibial cutting guides were machined from Delrin™, a bio-compatible plastic. The saw slots in the guides set the proximal/distal, flexion/extension, and varus/valgus alignment of the femoral and tibial components and were held in place with pins (Figure 3.2).

Figure 3.2 Image showing the high density plastic cutting blocks with slots for the saw and the centre of rotation set through the transcylindrical axis of the femur

Operative Procedure

Each patient received the standard trust antibiotic protocol of a pre-operative dose of gentamicin and teicoplanin. The operation was performed without the use of tourniquet under spinal anaesthetic. The Triathlon® Knee System with Otismed® ShapeMatch® technology was used for each TKA aiming for KA. A mid-line medial para-patellar approach was used with eversion of the patella. No soft tissue release was required in any patient. The patella was resurfaced on all occasions. Osteophytes

were not removed and the custom fit femoral guide was seated on the distal femur and on each occasion was found to sit satisfactorily, conforming to the patient's anatomy. The femoral cutting jig was fixed with two anterior and two distal pins. The distal femoral cut was made through the custom cutting guides to determine alignment. The standard Triathlon femoral cutting block was then used for the anterior, posterior and chamfer cuts. The tibial custom cutting jig was seated proximally and anteriorly with pins and was found to fit satisfactorily in all patients, again without resection of the osteophytes prior to the cuts. The tibial cut was made through the slot in the custom cutting guide.

Post-operatively

All patients had a drain left in the joint that was removed after 24hrs, as this was standard protocol in the unit at the time. The post-operative analgesia, mobilisation and physiotherapy regime was the same for all patients. Patients were followed up at 6 weeks post-operatively where HKA radiographs were performed.

The information from the 25 pre-operative MRI plans and HKA radiographs was collected and analysed and compared to post-operative HKA radiographs. For the HKA radiographs a digital radiograph detector with a 35cm x 35cm detector plate was used. Patients stood without footwear, with tibial tubercles facing forward. The tibial tubercle was used as positioning landmark as it is not distorted by OA. The X-ray beam was centred at the knee at a distance of 2.6m. The leg exposure had default coverage of 120cm and resulted in three images that were automatically stitched

together. Various joint angles and limb lengths had previously been determined as described by Cooke et al (Cooke et al. 1991). For this study the joint angles provided by the MRI plans were compared with the HKA radiographs, therefore the mechanical axis (MA), the Lateral Distal Femoral Angle (LDFA) and Medial Proximal Tibial Angle (MPTA) were measured using GE Medical Systems software. The MA was determined by measuring the angle intersecting a line drawn from the centre of the femoral head to the distal femoral sulcus and a line drawn from the centre of the tibial spines to the centre of the proximal surface of the talar dome. The LDFA and MPTA were determined as outlined in Figure 2.2. Reliability of angle measurement using this technique has previously confirmed high inter-reader reliability for HKA and other angles between the femur and tibia, and therefore I was responsible for all measurements (Sled et al. 2009). The paired t-test was used to determine the mean difference between the paired pre- and post- operative alignment values. P values smaller than 0.05 were considered significant. SPSS Version 22 (Armonk, NY: IBM Corp) and Excel 2016 was used for all analyses.

3.4 Results

All 25 patients had their pre-operative MRI scans and pre- and post-operative HKA radiographs analysed. The average age of the patients was 70 years old (range 47-85), 10 of the patients were male and 15 of the patients were female. Regarding the pre-operative MRI plans created from the Otismed® ShapeMatch® technology only one plan suggested an overall HKA of >3° from neutral MA. The plan in question was for a severe varus knee and proposed a MPTA of -6° and LDFA of 1° giving an

overall alignment of 5° of varus. The mean overall pre-operative HKA, LDFA and MPTA plans from the MRI scans are illustrated in Table 3.1 and are compared to the post-operative radiographs. Comparing all measurements in the pre- and post-operative groups there was no significant difference between the two ($P>0.05$). For the female subset the pre-operative MRI scan plans for HKA, LDFA and MPTA are compared with the post-operative radiograph measurements in Table 3.2. Again no significant difference was observed between the two groups. The male subset is illustrated in Table 3.3 and again there was no significant difference ($p>0.05$) in the alignment between the proposed MRI and post-operative radiographs.

The post-operative data demonstrated that only three patients were outwith 3° of the proposed MRI plans. Out of the three outliers one patient appeared to have an error in alignment from the femoral cutting block and the other two patients were outliers as a result of cumulative errors from both the femoral and tibial cutting blocks.

Although only three patients were technically outliers from the point of view of being >3° deviation from their plan, because the proposed MRI plans had a range of 5° varus to 3° valgus the actual post-operative range of alignment was from 6° varus to 5° valgus, this is illustrated in (Figure 3.3). Histograms of the pre- and post-operative LDFA and MPTA are shown in Figures 3.4 and 3.5.

Table 3.1 Mean pre-operative MRI scan plans and post-operative radiograph measurement parameters around the knee

Parameter	Pre-op MRI		Post-op XR		p-value*
	Mean	SD	Mean	SD	
HKA (°)	-0.44	1.73	-0.12	3.03	0.50
LDFA (°)	1.72	1.79	1.84	1.77	0.68
MPTA (°)	-1.96	2.21	-2.32	3.18	0.48

Table 3.2 Measurement parameters for female

Parameter	Pre-op Female MRI		Post-op Female XR		p-value*
	Mean	SD	Mean	SD	
HKA (°)	-0.67	1.80	-0.07	3.53	0.35
LDFA (°)	1.40	1.80	1.87	1.68	0.28
MPTA (°)	-1.80	2.60	-2.40	3.54	0.41

Table 3.3 Measurement parameters for male

Parameter	Pre-op Male MRI		Post-op Male XR		p-value*
	Mean	SD	Mean	SD	
HKA (°)	-0.10	1.66	-0.20	2.25	0.89
LDFA (°)	2.20	1.75	1.80	1.99	0.27
MPTA (°)	-2.20	1.55	-2.20	2.74	1.00

Values are expressed as mean +/- SD; HKA angle = hip-knee-ankle angle; LDFA = Lateral Distal Femoral Angle; MPTA = Medial Proximal Tibial Angle.

Figure 3.3 A histogram for HKA angle depicts the distribution of all 25 knees from the MRI scans pre-operatively and all 25 post-operative knees measured on radiograph

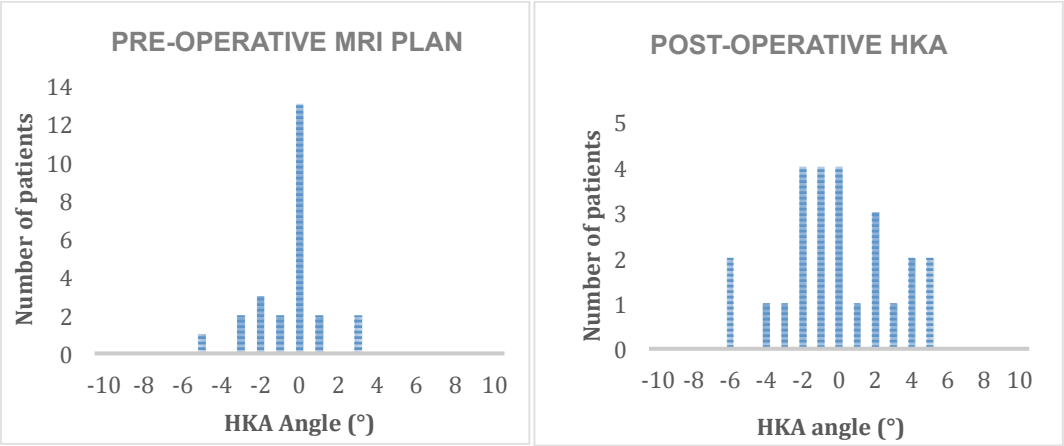


Figure 3.4 A histogram for LDFA for all 25 pre-operative knees for all post-operative knees

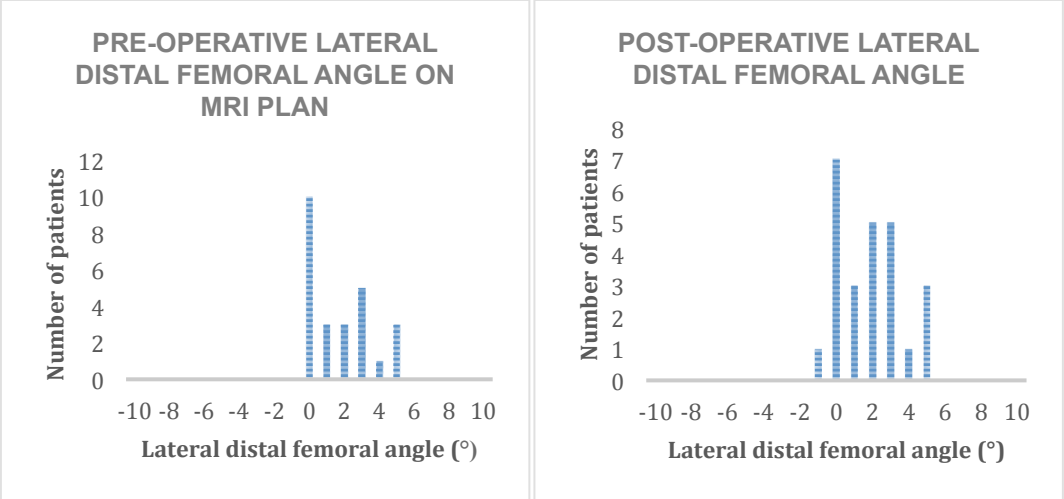
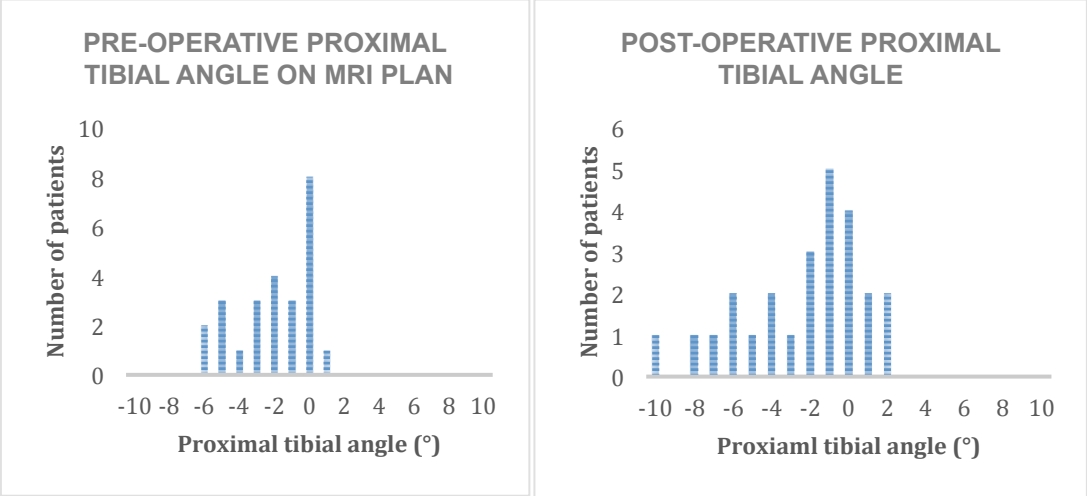


Figure 3.5 A histogram of MPTA of all knees from MRI plan pre-operatively and a comparative histogram of MPTA in all post-operative knees measured on HKA radiographs



3.5 Discussion

The first question from this initial case series was how the pre-operative MRI plans compare to previous population studies with regards to HKA, LDFA and MPTA. Bellemans work (Bellemans et al. 2012), introduced the idea on constitutional varus, with his population study showing 32% of men and 17% of women had constitutional varus knees with a natural mechanical alignment of 3° varus or more. Whilst the case series suggested that only three patients (12%) would have had a constitutional varus of ≥3° or more, patients were only considered for the study if their deformity was less than 10° valgus or varus in the coronal plane so this would have underestimated the figure in relation to the general population. Bellemans' overall HKA alignment for the population was 1.33° varus with a mean LDFA of 2.1° and mean MPTA -2.96°. The MRI plans for the case series had a mean HKA 0.44° varus with LDFA of 1.72° and MPTA of -1.96°, confirming a trend towards varus alignment and obliquity of the joint line.

The fact that only one of the pre-operative patient MRI plans aimed to restore overall alignment to beyond what has historically been regarded as acceptable parameters (HKA 0° +/- 3°) is reassuring. These results suggest that the alignment produced from the Otismed® ShapeMatch® technology does not, for the majority of patients, aim to create overall alignment in extremes of varus/valgus, and for patients with whom the MRI plans do suggest extremes (HKA >3° varus/valgus) there is the option to revert to neutral overall alignment if desired.

The second question from this initial proof of concept study was whether the patient specific cutting blocks delivered accurately the desired alignment cuts? The results found a strong correlation between the proposed pre-operative alignment and the post-operative alignment, suggesting that the cutting jigs were accurate. There was no significant difference in proposed MRI HKA pre-operative plan and post-operative alignment regarding the HKA, LDFA and MPTA parameters. Only three patients were >3° outwith the MRI plan. With regards to how this compares to outliers in other studies the results are favourable when compared to manual instrumentation (MI) but inferior to Computer Navigation (CN). Meta-analysis data published on CN versus MI has shown an average in overall malalignment of greater than 3° in 9% of patient using CN and 31.8% of patients when MI is used (Mason et al. 2007).

There are limitations when interpreting this study. Whilst a judicious and precise protocol was employed for the LLR, inaccuracy can occur if the x-ray is not centred on the knee and if there is tibial or femoral bowing, fixed flexion or rotation (Jiang & Insall 1989). 3D reconstruction CT is currently the most accurate method for measuring alignment (Hirschmann et al. 2011), but LLR were used as this can be utilised in everyday practice, is relatively inexpensive and readily available. Information on sagittal and rotational alignment was not assessed. As these were the first 25 patients in Europe to receive the technology there would have been a learning curve involved with familiarisation of the equipment.

This proof of concept study was the first in Europe to use the Otismed® ShapeMatch® technology (Stryker Corporation, Mahwah, NJ, USA, FDA clearance) and Otisknee™ custom cutting guides (Stryker Corporation, Mahwah, NJ, USA, FDA clearance). It has provided reassurance regarding the proposed MRI plans and correlation with population studies as well as demonstrating that the cutting blocks appeared to be reliable in producing the desired alignment.

Chapter 4 A Feasibility Study Comparing Kinematically Aligned Total Knee Arthroplasty with Mechanically Aligned Total Knee Arthroplasty.

4.1 Introduction

The results from the proof of concept study were encouraging regarding the use of the custom cutting blocks. The cutting blocks appeared safe and reproducible in trying to achieve the desired alignment from the MRI plans. The proof of concept study did not investigate patient outcome, so the next stage in the research process was to construct a feasibility study comparing the KA aligned TKAs with what was standard practice in the unit at the time. The feasibility study was designed to assess the Triathlon® TKA implanted in KA, with the Scorpio® implant in MA. The reason it was compared to Scorpio® was that of pragmatism in that the Scorpio® implant was the standard TKA used in the department at the time of the trial with data already being prospectively collected on patients who were receiving the implant. The Scorpio® implant is similar to the Triathlon® in that it has a single axis of rotation design to address mid-flexion instability by preserving ligament isometry maintaining a constant centre of rotation throughout the range of motion, providing uniform ligament tension during the transition from full extension to deep flexion (Mahoney et al. 2002). The Scorpio® has a proven track record in good long-term survivorship in studies. When implanted in MA the Triathlon® has demonstrated good mid-term survivorship results and good patient reported outcome measures (Scott et al. 2015). The primary aim of the feasibility study was to assess the potential for successful implementation of the Triathlon® Knee System with

Otismed® ShapeMatch® technology protocol and compare it to the standard TKA used in the unit at the time. The results of which were used to support the development of the RCT that was to follow.

The secondary aim of the feasibility study was to test the null hypothesis that there would be no difference in outcome between the two techniques, by seeing if a minimally clinically important difference (MCID) could be identified between the two cohorts, using the Oxford Knee Score (OKS) and the Western Ontario and McMaster Universities Arthritis Index (WOMAC). MCID is defined as the smallest change in an outcome that a patient could identify as important and could cause a clinician to alter management. The current accepted value reflecting a significance in the OKS has been demonstrated to be 3 points (Murray et al. 2007). The Oxford Knee Score was first published in 1998 (Dawson et al. 1998) and was developed as a new tool for the assessment of total knee arthroplasty outcomes. The score is derived from a 12-item questionnaire, which is self-administered by the patient. The questions were designed with input from patients in order to try to ensure that the information derived was as valid and sensitive as possible. The score has a range of 12 (least symptoms) to 60 (worst symptoms) and has been validated by comparison to the American Knee Society Clinical Rating Scale, the SF36 and the Stanford Health Assessment Questionnaire (Davies 2002). The change in OKS over time is considered a better representation of morbid status than absolute score over time (Murray et al. 2007; Price et al. 2010).

The WOMAC questionnaire was subjected to thorough psychometric validation processes before its introduction into clinical use for the assessment of interventions in management of osteoarthritis of the hip or knee (Bellamy et al. 1988). The WOMAC score is described on a scale from 0–100 where 0 represents the worst result and 100 represents the best. The MCID for the WOMAC in the context of TKA is been suggested to be around 15 points (Escobar et al. 2013), although in the context of the KOOS score, which is an extended version of the WOMAC score, the MCID is quoted as 8-10 points (www.KOOS.nu).

The only functional outcome measure in the feasibility study was that of range of motion. This was measured pre- and post-operatively by the patient's consultant with a universal goniometer. Only a few studies have reported the psychometric properties (such as reliability and validity) of knee ROM measurements using a universal goniometer in patients after TKA (Edwards et al. 2004; Käfer et al. 2004; Lenssen et al. 2007). Lenssen et al. (Lenssen et al. 2007) found that the inter-tester reliability was acceptable with regard to group comparison. Jakobsen (Jakobsen et al. 2010) reported that a real clinical improvement was a change of at least 6.6° between two measurements in knee ROM with a goniometer.

Previous studies have demonstrated a reduction in operative time and also a reduction in operative set-up time with custom fit cutting blocks, because the size of the components are known prior to the start of the operation (Spencer et al. 2009). A secondary outcome measure of this study was to assess operative time and number of surgical trays used.

The Royal Devon & Exeter NHS Foundation Trust Research and Development group granted local ethical approval (Appendix E).

4.2 Methods

Patients were recruited from the planned operating list of three consultant orthopaedic surgeons at the Exeter Knee Reconstruction Unit, Royal Devon and Exeter Hospital from December 2010 to April 2012. Patients were identified in the clinic prior to surgery and were provided with an information booklet that outlined what was involved in the trial. The booklet contained information about the Triathlon® Knee System with Otismed® ShapeMatch® technology. The inclusion/exclusion criteria for recruitment were the same as in the proof of concept case series.

Fifty consecutive patients (20 males and 30 females) were treated according to the Triathlon® Knee System with Otismed® ShapeMatch® technology protocol with the aim of producing cutting blocks to assist the surgeons to implant the prosthesis in KA (Stryker Corporation, Mahwah, NJ, USA). A further 50 patients were treated with the standard TKA used in the department at the time, the Stryker Scorpio® prosthesis (Stryker Corporation, Mahwah, NJ, USA) implanted in mechanical alignment using standard intra- and extra- medullary alignment guides. The two groups of patients were not randomised, but were matched in terms of pre-operative

baseline characteristics, this included age, sex and pre-operative WOMAC and OKS scores.

Pre-operatively all the ShapeMatch® patients underwent full-length lower limb radiographs (LLR) to assess alignment. MRI scans of the affected knee were undertaken using the protocol outlined in Chapter 3 to recreate an accurate model of the patient's pre-arthritic knee. The ShapeMatch® software determined the kinematic alignment of the knee for the purposes of implantation and the femoral and tibial component sizes. The images were then sent online for the surgeon to review, no corrections or alteration to the plans were made. The accepted coordinates of the prosthesis were transferred to the custom cutting guides that were then produced and sent to our institution prior to surgery.

Patients were assessed pre-operatively and then followed up at 6 weeks and 6 months post-operatively. Range Of Motion (ROM) was assessed using a goniometer by the consultant in clinic and patients filled out their own OKS and WOMAC outcome measures with a research physiotherapist (RS), which were then collated and scored and the figures were entered into a secure database.

The Triathlon® Knee System with Otismed® ShapeMatch® technology was used for each TKA aiming for KA and the operative technique for the KA cohort was exactly the same as previously documented Chapter 3. The second cohort of patients received Scorpio® Knee System (Stryker Corporation, Mahwah, NJ, USA). The same peri-operative antibiotic and anaesthetic technique was used as for the KA

group. No tourniquet was used, the same incision and approach was utilised and all patellae were resurfaced. Conventional cutting blocks with intra-medullary femoral and extra-medullary tibial instrumentation were used to assist the surgeon in achieving MA.

Post-operatively all patients had a drain left *in-situ* that was removed after 24 hours. The post-operative analgesia, mobilisation and physiotherapy regime were the same for both groups of patients. All patients received standard VTE prophylaxis protocol. Length of stay, use of transfusions, haemoglobin at discharge, and post-operative complications were recorded. All 100 patients were followed up and evaluated following the procedure.

Data was collected and analysed using SPSS Version 22 (Armonk, NY: IBM Corp) and Excel 2016. Patient reported outcome scores are presented as means with standard deviations (SD), with 95% confidence intervals. Differences between the two groups of patients were analysed using unpaired t-tests.

4.3 Results

Patient age, sex, OKS and WOMAC scores were recorded as matched baseline demographic data (Table 4.1). The pre-operative plans were accurate in predicting the femoral component size in 98% (n=49) of cases and on the one occasion the component was increased by one size it appeared unnecessary on post-operative radiograph. The operating surgeon elected to change the tibial component on five occasions; on review of the post-operative films this was the correct decision in two cases.

Table 4.1. Baseline Demographic and Clinical Characteristics

	Kinematic Alignment (N=50), mean and SD	**Mechanical Alignment (N=50), mean and SD**
Mean age	70 +/- 9.9	73 +/- 7.5
Female %	60	66
WOMAC	48 +/-14.2	45 +/- 11.3
OKS	39 +/- 6.9	40 +/- 7.4

Abbreviations: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; OKS, Oxford Knee Score; SD, Standard Deviation. WOMAC, 100 is best, 0 is worst. OKS, 12 is best, 60 is worst

The primary outcome measures are illustrated in Table 4.2. There was a significant improvement in the OKS at 6 months when comparing the ShapeMatch® TKA

group to the conventional TKA group (p=0.038 unpaired t-test) with a 4 point difference in OKS at 6 weeks 6 months between the two groups. A significant improvement was found at both 6 weeks and 6 months in the WOMAC score comparing the ShapeMatch® TKA with the conventional TKA (21 and 16 points respectively at 6 weeks p=0.031; 30 and 23 points respectively at 6 months p=0.027 unpaired t-test). The WOMAC score was 8 and 10 points higher in the KA group compared to the MA at 6 weeks and 6 months respectively.

Table 4.2 Primary Outcome Measures

Parameter	KA		MA		Mean Difference	95% CI		p-value*
	Mean	SD	Mean	SD		Lower	Upper	
WOMAC								
6 weeks	69.0	15.5	61.0	18.0	8.0	0.8	15.9	**0.03**
6 months	78.0	17.1	68.0	23.0	10.0	1.1	18.1	**0.03**
OKS								
6 weeks	28.0	8.7	32.0	10.0	4.0	-7.3	1.0	0.14
6 months	22.0	10.0	26.0	11.0	4.0	-8.8	-0.2	**0.04**

Abbreviation: CI, confidence interval; SD, standard deviation

The secondary outcome measures are illustrated in Table 4.3. The changes in haemoglobin (p=0.5) and in ROM at 6 months (p=0.7) were not significantly different between the two methods of alignment. The operative time in the ShapeMatch® group was 15 minutes less than in the Scorpio® group (p<0001). The mean length of inpatient stay was 3.7 days in the ShapeMatch® group and 5.2 days

with the conventional group. The mean number of instrument sets used was five for the ShapeMatch® group versus 11 in the conventional group.

Table 4.3 Secondary Outcome Measures

Parameter	KA		MA		Mean Difference	95% CI		p-value*
	Mean	SD	Mean	SD		Lower	Upper	
Operation Time (min)	65.0	17.3	79.0	17.0	14.0	-23.0	8.0	**0.0001**
Change in Hb (g/dl)	3.1	1.0	3.2	1.0	0.1	-0.3	0.5	0.5
Length of inpatient stay (days)	3.7	2.6	5.2	2.2	1.5	-2.0	-1.0	**0.0001**
Change in ROM 6 months (°)	13.4	14.3	14.2	14.9	0.8	-5.0	5.0	0.76

Abbreviation: CI, confidence interval; SD, standard deviation

Complications

Within the ShapeMatch® group three complications occurred. One patient developed cellulitis around the wound that responded to oral antibiotics. One patient fell on the ward at day two post-operation and as a result required two extra days physiotherapy as an inpatient. One patient developed post-operative hyponatraemia and delirium, fell and suffered wound dehiscence that was debrided and closed 1 week following initial surgery. From the Scorpio group, one patient required evacuation of a haematoma.

4.4 Discussion

The primary purpose of this study was to assess the feasibility of running a future RCT using the Triathlon® Knee System with Otismed® ShapeMatch® technology with the inclusion and exclusion criteria used in Chapter 3. It took 17 months to recruit 50 patients for the KA TKAs, which is acceptable. It also provided the surgeons with experience using the new device before the RCT. The secondary outcome measure was to see if there was any difference in outcome between the two cohorts of patients. There was a significant difference in terms of statistical paired t-tests between the two groups, this translated to a MCID for the OKS (4 points) and for the WOMAC score (10 points).

Importantly there were no major complications regarding the custom fit cutting blocks that all conformed to the patient's anatomy. The one patient who had the wound dehiscence did not subsequently developed a deep infection, and the complication was not attributable to the new technology. There were however significant improvements in the patient reported outcome measures at both 6 weeks and 6 months. This was an exciting development because whilst Computer Navigation has been proved to increase accuracy of desired alignment (Mason et al. 2007), this has not correlated with improved patient reported outcomes (Spencer et al. 2007). There are some possible explanations for the improved outcomes in the study. By placing the implants in kinematic alignment no soft tissue release was performed on any of the ShapeMatch® patients. This was because both the femoral

and tibial cuts recreated the natural joint line and the pre-operative MRI accurately determined the flexion and extension axis. This may have reduced post-operative pain, therefore improving the pain component of the WOMAC score. The KA may have given a more natural feel to the implant resulting in an increase in the functional component of the OKS and WOMAC scores.

The was no difference in blood loss between the two groups in the study indicating that penetrating the femoral canal with an intra-medullary guide does not cause a significant loss of haemaglobin. The reduction in operating time is unequivocal and the 15 minute reduction is similar to that found in early studies utilising PSI (Barrack et al. 2012; Dossett et al. 2012; Spencer et al. 2009).

The reduction in length of inpatient stay may be significant. When comparing the two groups of patients, they both received the same anaesthetic and peri-operative analgesia regime. Once the surgeon was content the patient was fit for discharge it was left to the physiotherapist and occupational therapist to ensure the patient was safe to go home, this should have protected against bias, as the rehab team were not informed about the trial of ShapeMatch® knees. The patients appeared to have less pain post-operatively, were able to mobilise more rapidly, and anecdotally reported that the knee felt more stable. The theoretical reason for this is again the lack of soft tissue release with kinematic alignment.

There are limitations to this study. This was only a feasibility study and importantly the patients were not randomised. The ShapeMatch® group were compared to what was standard practice in the institution. There are subtle differences between the Triathlon® and Scorpio® knee replacement. They are based on the same philosophy of a single radius of curvature. The Scorpio® has a single radius of curvature from 10° to 70° and a single medial/lateral radius whereas the Triathlon® has a single radius of curvature from 10°-110°. The Triathlon® system has flared posterior condyles designed to accommodate 20° of internal/external rotation throughout the range of motion as well as a 7° anterior flange. The positive findings of accuracy of sizing of the implant and reduction in operative time are independent of the design of the prosthesis. Without randomisation and blinding there would been selection bias when comparing the two groups. The Scorpio® group were informed that they were receiving a standard knee replacement, where as the ShapeMatch® group may have had raised expectations and motivation in the knowledge that they were receiving new technology, although the patients were informed pre-operatively that it was not known whether either technique was superior.

This was the first European cohort of patients to have received a TKA with the new kinematic alignment technique with 6 months follow-up. There were no major complications directly attributable to the new technique. Compared to our standard practice there was a statistical improvement in patient reported outcomes at both 6 weeks and 6 months. The 4 point difference in OKS and 10 points for the WOMAC represents a MCID.

Chapter 5 The Early Outcome of Kinematic versus Mechanical Alignment in Total Knee Arthroplasty. A Prospective Randomised Control Trial

5.1 Introduction

The proof of concept and feasibility study had provided adequate results to aid the construction of an RCT. The computer software and cutting blocks appeared to deliver accurate and reproducible results. The clinical results of Triathlon® TKA implanted in KA appeared to be at least comparable to the Scorpio® TKA implanted in MA when looking at the OKS and the WOMAC scores. The primary aim of this study was to compare KA versus MA in a randomised group of patients to see if the different types of alignment influenced overall patient outcome when using the same prosthesis.

The secondary aim of the study was to compare the established generic and joint specific patient reported outcome measures (PROMs) with functional assessment tests performed by the patient pre- and post-operatively in a controlled physiotherapy environment, and look at their correlations to see if there were differences in the qualitative and quantitative data and test reliability and responsiveness (Beard et al. 2010; Garratt et al. 2001; Dunbar et al. 2001).

The null hypothesis was that there would be no difference in outcome between the KA group and MA group of patients.

5.2 Methods

Trial design

The RCT was designed to compare the Otismed® Custom Fit cutting blocks with the Triathlon® TKA using ShapeMatch® software implanted in KA (Stryker Corporation, Mahwah, NJ, USA, FDA clearance) with the Triathlon® TKA implanted in MA using conventional intra- and extra- medullary alignment guides. The study was originally set up as part of an international study with Hanover. The choice of which PROMs to use was dictated to us by the Hanover group. This explains why there is a difference between the PROMs used in the feasibility study and the PROMs used in the RCT. After induction of the study the Hanover Centre withdrew due to a low recruitment rate prior to a device recall. Regarding the device recall, Stryker Corporation stopped the manufacturing of the Otismed® Custom Fit cutting blocks in April 2013 due to concerns raised by some American surgeons regarding the accuracy of the cutting blocks. The proof of concept and feasibility study did not raise such concerns with the cutting blocks at the study unit. The impact of the device recall on this study was that seven patients who were recruited to the study had to be withdrawn, as they had not received their intervention before the recall date.

Participants

Patients were recruited from the waiting list of three consultant orthopaedic surgeons (ADT, VIM, KSE) between December 2011 and April 2013. All three surgeons had

performed at least 25 ShapeMatch® TKAs by the time of the trial and were proficient with the use of the Triathlon® implant. The inclusion and exclusion criteria were the same as for the previous studies. Appropriate patients were identified in a dedicated knee arthroplasty clinic. The nature and requirements of the trial were clearly explained to them as well as discussion regarding the implants that would be used. The patients who entered the trial were given a booklet outlining the details of the surgery and follow-up requirements.

Interventions

The operative technique was the same as in the feasibility study. Patients in the KA group had MRI scans pre-operatively. The surgeon was then sent a surgical plan with the proposed alignment specific for each patient according to his or her own KA. No corrections were made to the plan before the patient-specific cutting blocks were made. The TKAs were performed either with the patient-specific cutting blocks to achieve KA or with standard extra and intramedullary instrumentation to achieve MA. A medial para-patellar approach without the use of a tourniquet was used. The cemented Stryker Triathlon® (Stryker Corporation, Mahwah, NJ, USA, FDA clearance) cruciate retaining knee system with patellar resurfacing was used in both groups. The post-operative protocol was identical for both groups.

Outcomes

All patients were reviewed at a pre-operative clinic and at 6 weeks, 3 and 6 months and 1 year post-operatively by a research physiotherapist, Rowenna Stroud (RS) who was blinded to the patients' treatment modality. The patients had to fill in generic and joint specific PROMs, these included:

- SF-36
- EQ-5D
- UCLA
- KOOS

The physiotherapist was responsible for scoring the functional tests, these included:

- The AKSS
- Timed-up and go
- Timed 2 minute walk
- Timed up and down stairs (Figure 5.1)
- Quads and hamstring strength measured with a myometre (Figure 5.2 and 5.3)
- Walking on an uneven surface
- Walking up and down a slope
- Balance using the Wii-fit

Figure 5.1 Showing the rig used for the Timed up and down stairs test

Figure 5.2 Photograph demonstrating measurement from the tibial tubercle 30cm distally with the leg hanging at 90° for measurement of peak quadriceps torque

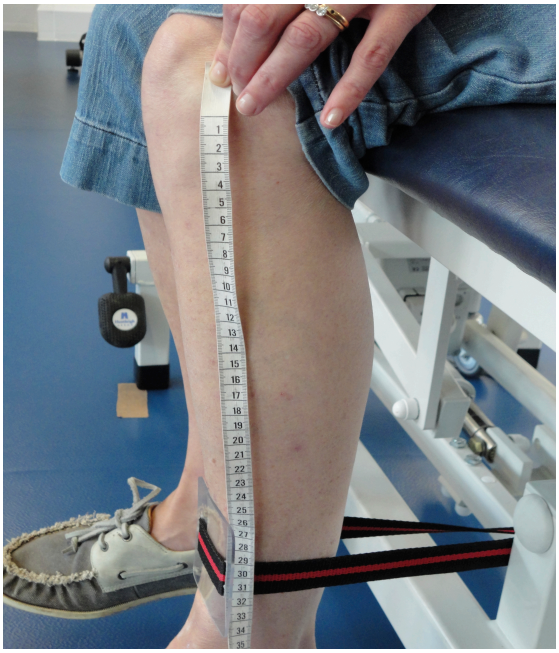


Figure 5.3 Photograph demonstrating measurement of peak hamstring torque

Sample size

Using the results from the feasibility study, the RCT was powered to demonstrate a 10 point difference in the WOMAC score, which is an abridged version of the KOOS score. The MICD for the KOOS is currently suggested to be 8-10 (www.koos.nu) Assuming a 15 point pre-operative standard deviation in the score (www.koos.nu) a size effect of 0.66 was used to power the study. It should be noted that the pre-operative standard deviation in the control group was 11 in the feasibility study, but 18 and 23 at 6 weeks and 6 months postoperatively. Using a one tailed analysis (assuming superior results with the KA group) and an alpha of 0.05 with a power of 0.80, 60 patients (30 in each arm) were required. Assuming a 15% loss to follow-up at 1 year, a total of 70 patients needed to be recruited.

Randomisation

Following consent to the trial the patients were then randomised using a true random number generator program. Cards displaying the numbers 1 (for KA) or 2 (for MA) were placed in sealed envelopes. The patients were allocated an envelope that was opened in sequence

Blinding

A research physiotherapist was blinded to the treatment modality each patient had received, carried out the functional assessment of the patients. It was not possible,

due to financial constraints, to blind the patients to their treatment, as those in the MA group did not receive an MRI scan. The surgeons were not blinded to the intervention, as the cutting blocks were different between the two groups.

Statistical methods

The functional assessment and patient reported outcome scores are presented as means with standard deviations (SD), with 95% confidence intervals. Differences between the two groups of patients were analysed using unpaired t-tests for improvement at four time points after surgery. For correlation between outcome assessments non-parametric distribution was tested by the Shapiro-Wilk test of normality. The Spearman's rank-order correlation was used to assess the relationships. SPSS version 22 software was used (SPSS Inc., Chicago, Illinois) for analysing the results. A p-value ≤ 0.05 was defined as clinically significant.

Ethical approval for this study was obtained from the National Research Ethics Service Committee Cambridge East and by the Royal Devon and Exeter Foundation Trust Research and Development team (Appendix E).

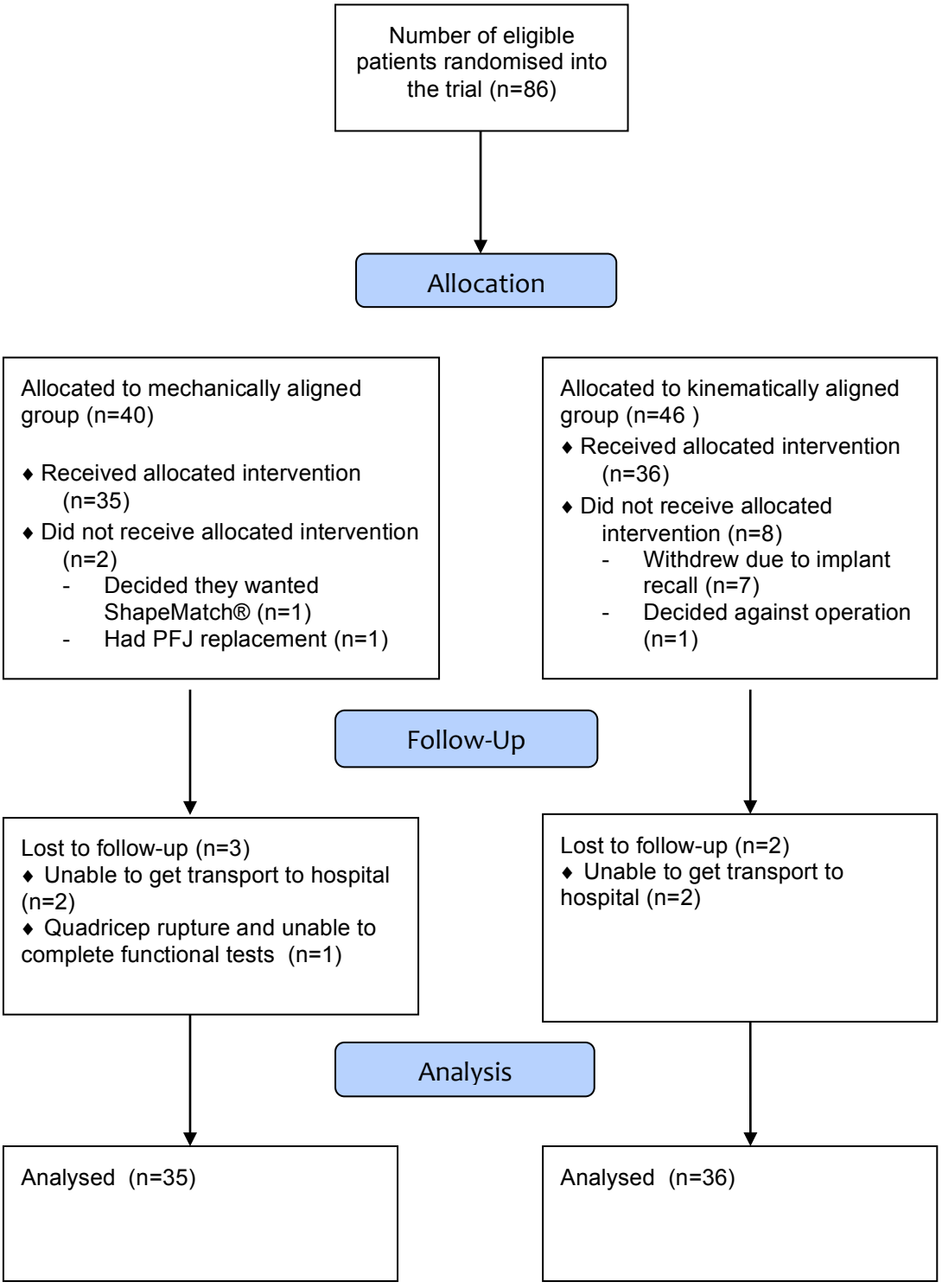
5.4 Results

Follow-up and patient withdrawal

A flow diagram of the patients in the study, according to the CONSORT Guidelines is shown in Figure 5.4. A total of 86 patients fulfilled the criteria and were recruited into the study. Of these 71 (83%) underwent surgery and were followed up for one year. Seven patients in the KA group were recruited but were withdrawn due to a medical device Class I recall in April 2013. Five patients were lost to follow-up. One patient decided not to have an operation, one patient opted for a patellofemoral replacement and one decided they wanted a KA TKA, and so withdrew. One patient sustained a post-operative rupture of the extensor mechanism and was withdrawn from functional assessment.

Thirty-six patients received the ShapeMatch® technology and 35 patients received the Triathlon® TKA in mechanical alignment. In the ShapeMatch® group 13 patients were females (36%) and 23 were male (64%) with an average age of 75 years. In the Triathlon group 20 patients were females (57%) and 15 patients were males (43%) with an average age of 75 years.

Figure 5.4 Flow Diagram of recruitment and follow up



Flow diagram of participants according to the CONSORT guidelines

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Alignment

The pre-operative alignment plans for the KA group ranged from 7° of varus to 7° of valgus with 78% (28 patients) within 3° of neutral overall alignment (Figure 5.5). The mean lateral distal femoral angle (LDFA) in the pre-operative plan for the KA group was 88° (83° to 92°) and the mean medial proximal tibial angle (MPTA) was 87° (80° to 93°). A total of 28 patients (78%) (Figure 5.6) in the KA group and 27 (77%) (Figure 5.7) in the mechanically aligned group had their post-operative alignment within 3° of the MRI plan or neutral overall alignment respectively.

Figure 5.5 Graph illustrating overall MRI alignment plans for the KA group

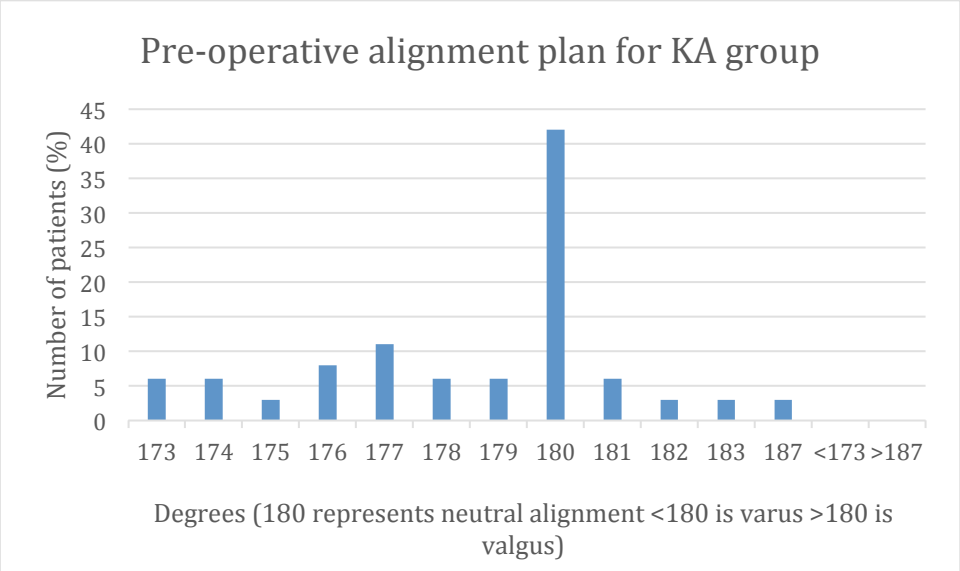


Figure 5.6 Graph illustrating the distribution of post-operative overall alignment in the KA group.

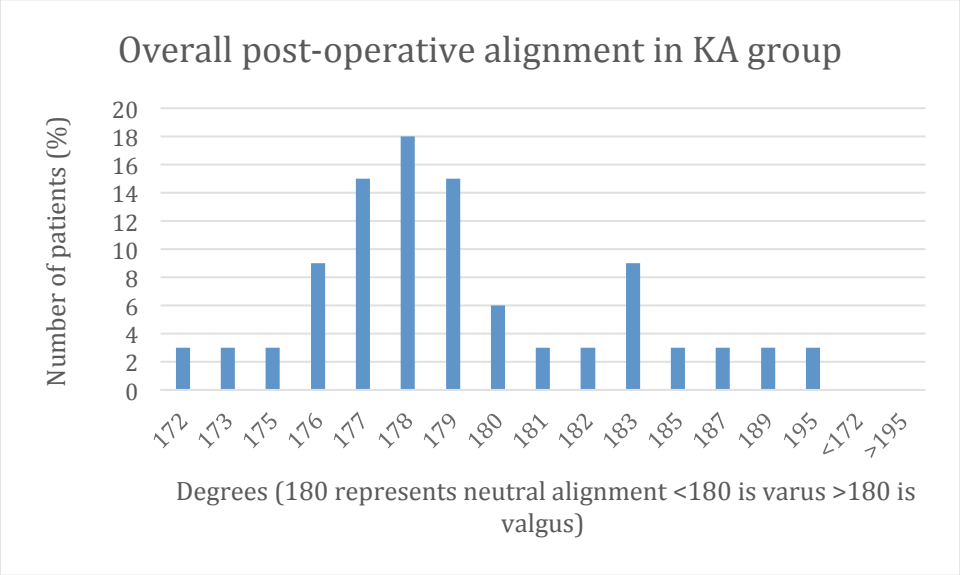
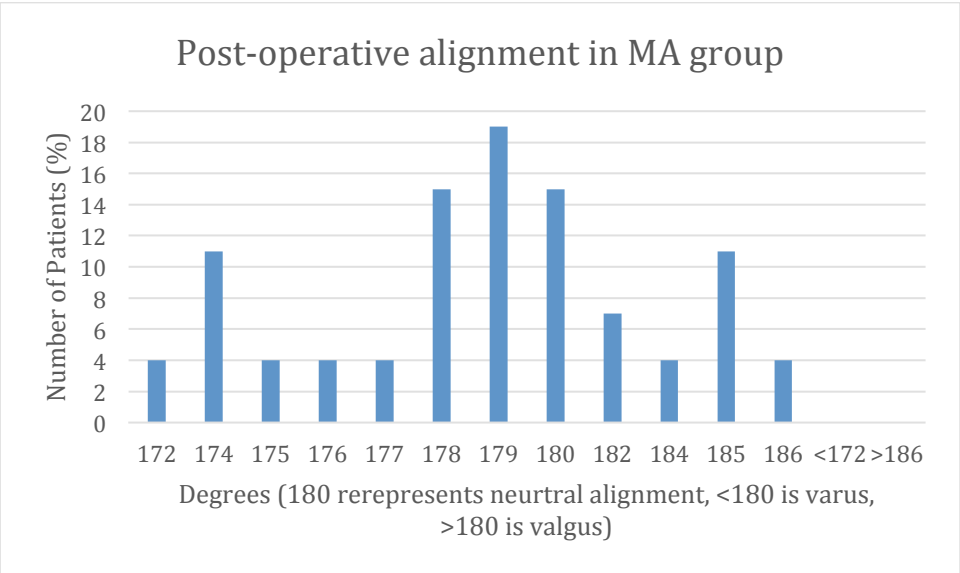


Figure 5.7 Graph illustrating the distribution of post-operative alignment in the MA group.



Generic quality of life scores

The generic outcome scores are shown in Table 5.1. The corresponding bar charts with confidence intervals and all eight domains from the SF-36 are illustrated in Appendix C. There was a consistent improvement from pre-operative levels through to 1 year post-operatively in both the KA and MA groups. Regarding the SF-36 all domains were matched pre-operatively between the two groups except that of physical function, which was better at base line in the KA group. Better pre-operative function in the KA group was also seen in a number of the other functional tests. All patients were randomised so this finding was unexpected. It could represent a Type I error, where in fact no relationship existed. The finding was certainly not universal in the pre-operative tests. The patients themselves were not blinded to the treatment modality, and having been randomised to the kinematic group, this could have raised their expectations and been a motivating factor, improving some components tested. The SF-36 did show a significant improvement in the KA group versus the MA group at 6 months post-operation. On close inspection of the results, this appears to be due to a reduction in the mean SF-36 score in the MA group at the 6 month follow up in comparison to their 3 month results, this result can be assumed to be an anomaly. The EQ-5D did not demonstrate any difference between the two groups pre-operatively or at any stage in the post-operative period. Like the SF-36 the UCLA scores were better pre-operatively in the kinematic group but no significant difference was observed in the post-operative period.

Table 5.1. Generic patient reported outcome measures.
Post-operative University of California, Los Angeles activity score, Short Form-36 and EuroQol-5D scores

PROM	KA		MA		Mean Difference	95% CI		p-value*
	Mean	SD	Mean	SD		Lower	Upper	
SF-36 PF								
Pre-op	44.0	22.5	30.1	17.4	13.9	4.2	23.5	**0.01**
6 weeks	51.0	22.7	48.8	21.0	2.2	-11.0	15.4	0.74
3 months	70.0	20.7	62.8	22.0	7.2	-5.2	19.6	0.25
6 months	73.8	24.3	58.8	27.6	15.1	0.9	29.2	**0.04**
1 year	73.8	24.0	68.5	24.8	5.3	-8.6	19.2	0.45
EQ-5D								
Pre-op	69.8	17.1	63.4	16.8	6.4	-2.3	15.1	0.15
6 weeks	52.5	39.0	56.8	34.6	-4.3	-22.3	13.7	0.63
3 months	61.4	41.5	65.5	30.5	-4.2	-22.2	13.9	0.65
6 months	69.3	30.9	71.7	26.0	-2.4	-16.7	11.8	0.73
1 year	79.5	12.9	78.6	19.0	0.9	-7.9	9.6	0.84
UCLA								
Pre-op	4.5	1.6	3.7	1.2	0.8	0.1	1.5	**0.02**
6 weeks	4.0	1.8	4.2	1.2	-0.2	-1.0	0.7	0.67
3 months	5.3	1.3	4.8	1.7	0.5	-0.5	1.4	0.32
6 months	5.8	1.7	5.5	1.7	0.3	-0.6	1.2	0.54
1 year	5.7	1.9	5.6	1.6	0.1	-0.9	1.1	0.84

* Unpaired t-test. KA, kinematically aligned; MA, mechanically aligned; PROM, patient-reported outcome measure; SD, standard deviation;
CI, confidence interval

Joint specific outcome measures

The KOOS score demonstrated that the KA group had improved mean scores pre-operatively (p=0.01) but that at all stages in the post-operative assessment there was no significant difference between the two groups. For the AKSS both groups were matched at baseline (p=0.29). There was a greater improvement in the mean AKSS in the KA group at 6 weeks when compared with the MA group (p=0.05), but at 1 year there was no significant difference (p=0.42).

Table 5.2. Joint specific outcome measures. American Knee Society Score and Knee Injury and Osteoarthritis Outcome Score.

PROM	KA		MA		Mean Difference	95% CI		p-value*
	Mean	SD	Mean	SD		Lower	Upper	
KOOS								
Pre-op	45.5	11.0	36.8	12.9	8.8	2.2	15.3	**0.01**
6 weeks	59.0	15.0	59.0	15.7	0.0	-8.8	8.9	0.99
3 months	74.3	13.2	69.8	16.0	4.5	-3.9	12.9	0.29
6 months	74.7	20.7	70.7	16.3	4.1	-5.7	13.9	0.41
1 year	77.7	20.0	76.4	19.0	1.3	-9.4	12.1	0.80
AKSS								
Pre-op	57.5	18.5	53.5	11.3	4.0	-3.5	11.5	0.29
6 weeks	65.7	13.1	59.0	9.2	6.7	0.1	13.2	**0.05**
3 months	78.4	21.1	69.1	17.5	9.3	-1.6	20.1	0.09
6 months	79.8	21.3	77.0	19.8	2.8	-8.5	14.0	0.62
1 year	83.5	21.4	87.8	15.9	-4.3	-14.9	6.3	0.42

* Unpaired t-test. KA, kinematically aligned; MA, mechanically aligned; PROM, patient-reported outcome measure; SD, standard deviation;
CI, confidence interval

Functional outcome tests

The results of the physical function tests showed a similar trend and are shown in Table 5.3. There was no significant difference in the TUG test, the Two minute walking distance test and the Timed up and down stairs test at any stage post-operatively between the two groups. The measurements of peak torque in the quadriceps were significantly better in the KA group at 6 weeks and 3 months ($p= 0.003$ and $p=0.02$, respectively) but were not significantly different 1 year post-operatively. The peak torque in the hamstrings was weaker at 6 weeks, 3 months and 6 months post-operatively in both groups than at the pre-operative stage before improving at the 1 year mark. Range of motion was matched pre-operatively ($p=0.19$) and was reduced in comparison to the pre-operative range of motion at 6 weeks post-operative, but then improved in both groups up to 1 year post-operatively with no significant difference between the two groups, both finishing with a range of 118°

Table 5.3 Functional outcome tests.

PROM	KA		MA		Mean Difference	95% CI		p-value*
	Mean	SD	Mean	SD		Lower	Upper	
TUG								
Pre-op	12.4	6.5	15.6	8.0	-3.2	-6.7	0.3	0.08
6 week	10.9	5.2	12.3	5.0	-1.4	-4.3	1.5	0.35
3 month	8.5	2.7	9.8	3.2	-1.3	-3.0	0.3	0.11
6 month	8.9	3.1	10.2	5.0	-1.3	-3.6	1.1	0.29
1 year	9.8	7.6	9.1	2.8	0.8	-2.3	3.9	0.62
Two minute								
Pre-op	105.8	43.9	81.6	34.6	24.2	5.0	43.4	0.01
6 weeks	112.1	35.7	96.2	29.9	15.9	-2.8	34.5	0.09
3 months	137.0	33.5	111.9	30.7	25.0	7.5	42.6	0.01
6 months	131.4	52.1	112.4	37.6	19.0	-4.8	42.8	0.12
1 year	137.4	50.5	157.4	181.6	-20.0	-92.8	52.8	0.58
Timed stairs								
Pre-op	20.1	12.5	27.8	14.4	-7.7	-14.2	-1.1	**0.02**
6 weeks	22.5	13.2	21.6	10.4	0.9	-5.8	7.6	0.79
3 months	14.2	5.8	17.2	8.6	-3.1	-7.3	1.1	0.15
6 months	16.1	9.6	19.5	17.8	-3.4	-11.3	4.5	0.39
1 year	13.8	10.5	16.3	9.1	-2.4	-7.8	2.9	0.37
Peak torque in quadriceps								
Pre-op	61.0	39.9	52.5	36.0	8.6	-16.5	33.6	0.49
6 weeks	65.8	23.0	43.3	19.0	22.5	8.4	36.7	**0.00**
3 months	67.3	26.6	51.2	23.7	16.1	2.2	30.1	**0.02**
6 months	74.5	35.4	58.0	26.2	16.6	-0.6	33.8	0.06
1 year	80.6	33.6	69.9	27.4	10.7	-8.2	29.6	0.26

Table 5.3 Functional outcome tests continued.

PROM	KA		MA		Mean Difference	95% CI		p-value*
	Mean	SD	Mean	SD		Lower	Upper	
Peak torque in hamstrings								
Pre-op	39.0	19.8	32.7	20.2	6.3	-6.7	19.4	0.33
6 weeks	31.4	13.7	25.3	13.3	6.1	-3.2	15.4	0.19
3 months	33.4	12.0	26.0	10.3	7.4	1.3	13.5	**0.02**
6 months	36.8	27.2	30.1	12.2	6.7	-4.8	18.1	0.25
1 year	40.5	18.0	33.5	13.9	7.0	-2.7	16.8	0.15
Range of motion								
Pre-op	111.2	17.1	106.2	13.8	5.1	-2.5	12.7	0.19
6week	104.0	14.9	100.8	24.1	3.2	-8.9	15.3	0.60
3month	111.7	13.3	110.3	14.1	1.4	-6.4	9.2	0.72
6month	116.9	9.7	116.8	9.3	0.1	-5.1	5.3	0.97
1year	118.5	12.0	118.4	9.4	0.1	-6.1	6.2	0.98

* Unpaired t-test. KA, kinematically aligned; MA, mechanically aligned; SD, standard deviation; TUG, timed up-and-go; CI, confidence interval

Further functional assessment

The full results and statistical output from the remaining functional tests are illustrated in Appendix C. The ability of the patient to balance as measured on the Wii Fit™ was not significantly different at any time point between the two groups. The ability of the patients to kneel was no different between the two groups. In the KA group 66% of patients could kneel pre-operatively and this figure had increased to 81% one year post-operatively. In the MA group 60% of patients could kneel pre-operatively versus 85% of patients at 1 year. Although there were no differences between the two groups it does demonstrate that it is easier to kneel after a TKA than before the operation.

The gradient at which the patients felt comfortable walking up hill on a tread mill was matched at baseline but at 1 year the KA group were able to manage a mean gradient of 15.0° in comparison to 13.7° in the MA group ($p=0.05$). The gradient for walking down hill was significantly better in the KA group at 3 months (14.8° vs 12.9°, $p=0.05$) but there was no difference at 1 year.

Regarding the question 'Do you feel like you have forgotten that you have an artificial knee?' at 6 weeks post- operation 21% of KA patients had forgotten versus 36% of MA patients and at 1 year 59% of KA patients had forgotten about their knee in comparison to 44% of the MA group. This did not represent a significant difference. The ability of the patients to walk on an uneven pebbled surface improved from pre-operative through to 1 year post-operation but there was no significant differences between the two groups. Pains scores improved in both groups

in the post-operative period but there was no significant difference at any time point between the two groups.

A subgroup analysis was performed comparing those in the two groups whose post-operative radiographs were within 3° of their plan (Table 5.4). The mean peak torque in the hamstrings was significantly greater at 1 year in the KA group (p=0.04). There was a trend towards the patients in the KA group having forgotten they had a TKA although this did not reach significance (77% versus 45%, p=0.10, 95% CI 0.8 to 8.2). Further assessment comparing the functional outcome at 1 year of patients within 3° of planned alignment and those outside 3° in the KA group is shown in Table 5.5. Again peak torque in the hamstrings was significantly greater at 1 year in the group that was within 3° of the planned KA.

Table 5. 4 Comparison of functional assessments measured at 1 year for patients within 3° of planned alignment, comparing KA with MA groups.

Functional Assessment		Planned KA (n=26)		Planned MA (n=21)		Difference	95% CI		p-value
		Mean	SD	Mean	SD		Lower	Upper	
UCLA		6.0	1.9	5.6	1.6	0.4	-0.6	1.4	0.42
KOOS		79.3	17.0	76.4	19.0	2.9	-7.8	13.7	0.58
Function Score		87.1	22.4	87.8	15.9	-0.7	-12.4	10.9	0.90
PROM Range		120.0	9.5	118.4	9.4	1.6	-4.3	7.5	0.59
EQ5D-HS		81.0	12.6	78.6	19.0	2.4	-7.3	12.0	0.62
PainScore		1.6	1.8	1.9	1.1	-0.2	-2.0	1.5	0.78
TUG Time		9.4	8.3	9.1	2.8	0.3	-3.1	3.8	0.85
2 min Dist		146.2	51.7	157.4	181.6	-11.2	-93.6	71.2	0.79
Peak Tq Quads		88.1	33.9	69.9	27.4	18.2	-1.8	38.2	0.07
Peak Tq Hams		44.3	18.0	33.5	13.9	10.9	0.6	21.1	**0.04**
SF-36	**PF**	72.4	23.3	75.8	23.2	-3.4	-18.3	11.5	0.65
	RP	70.2	27.9	71.1	21.5	-0.8	-16.9	15.3	0.92
	RE	82.5	24.1	85.5	20.6	-3.0	-17.4	11.4	0.68
	SF	46.4	10.6	45.8	7.4	0.6	-5.4	6.6	0.84
	MH	62.6	11.6	65.8	8.4	-3.2	-9.7	3.4	0.33
	EV	49.7	13.3	51.6	12.3	-1.9	-10.2	6.3	0.64
	Pain	39.0	33.3	26.5	21.6	12.5	-7.1	32.1	0.20
	GH	53.1	12.3	49.5	15.2	3.6	-5.2	12.4	0.41
	CH	28.6	25.4	33.3	25.7	-4.8	-21.4	11.9	0.56

KA, kinematically aligned; MA, mechanically aligned; CI, confidence interval; SD, standard deviation; UCLA, University of California, Los Angeles; KOOS, Knee Injury And Osteoarthritis Outcome Score; PROM, patient-reported outcome measure; EQ, EuroQol; TUG, timed up-and-go; Tq, torque; quads, quadriceps; hams, hamstrings; SF, short-form; PF, Physical Health; RP, Role-Physical; RE, Role-Emotional; SF, Social Functional; MH, Mental Health; EV, Emotional Vitality; GH, General Health; CH, Change Health

Table 5.5. Comparison of functional assessments measured at 1 year for the KA group, comparing those within 3° of planned alignment and those outwith 3° of planned alignment (incorrect).

Functional Assessment		Planned KA (n=26)		Incorrect KA(n=7)		Difference	95% CI		p-value
		Mean	SD	Mean	SD		Lower	Upper	
UCLA		6.0	1.9	4.4	1.1	1.6	-0.2	3.4	0.82
KOOS		79.3	17.0	82.8	20.0	-3.4	-23.1	16.2	0.72
Function Score		87.1	22.4	76.3	17.0	10.8	-14.3	35.9	0.38
PROM Range		120.0	9.5	123.8	2.5	-3.8	-14.0	6.5	0.45
EQ5D-HS		81.0	12.6	77.0	8.4	4.0	-8.3	16.3	0.51
PainScore		1.6	1.8	1.3	1.2	0.3	-2.3	2.9	0.81
TUG Time		9.4	8.3	10.3	1.6	-0.9	-9.7	7.9	0.83
2 min Dist		146.2	51.7	110.0	14.1	36.2	-18.5	90.9	0.18
Peak Tq Quads		88.1	33.9	51.9	8.6	36.2	0.2	72.3	**0.05**
Peak Tq Hams		44.3	18.0	28.0	7.9	16.3	-3.1	35.7	0.10
SF-36	**PF**	72.4	23.3	46.7	27.0	25.7	2.8	48.6	**0.03**
	RP	70.2	27.9	60.4	22.9	9.8	-15.9	35.6	0.44
	RE	82.5	24.1	72.2	26.7	10.3	-13.2	33.8	0.37
	SF	46.4	10.6	45.8	17.1	0.6	-11.0	12.2	0.92
	MH	62.6	11.6	65.0	11.8	-2.4	-13.5	8.7	0.66
	EV	49.7	13.3	52.1	7.6	-2.4	-14.2	9.4	0.68
	Pain	39.0	33.3	52.1	29.0	-13.1	-45.1	18.8	0.40
	GH	53.1	12.3	50.8	11.1	2.3	-9.2	13.8	0.69
	CH	28.6	25.4	29.2	29.2	-0.6	-25.5	24.4	0.96

KA, kinematically aligned; MA, mechanically aligned; CI, confidence interval;SD, standard deviation; UCLA, University of California, Los Angeles; KOOS, Knee Injury And Osteoarthritis Outcome Score; PROM, patient-reported outcome measure; EQ, EuroQol; TUG, timed up-and-go; Tq, torque; quads, quadriceps; hams, hamstrings; SF, shortform; PF, Physical Health; RP, Role-Physical; RE, Role-Emotional; SF, Social Functional; MH, Mental Health; EV, Emotional Vitality; GH, General Health; CH, Change Health

Correlation between tests

The final aspect of the results was to compare correlations between the joint specific outcome measures, generic outcome measures and functional tests. For ease of comparison the outcome measures with a monotonic relationship, as assessed by visual inspection of a scatterplot, were used.

Table 5.6. Correlation between pre-operative and 1 year post-operative Two minute walk test and other functional tests.

Spearman's rho		Pre-op TUG	Pre-op Stairs	Preop Quad	Preop Hamstring	Preop ROM
Pre-op 2 min distance	R_s	-0.90	-0.77	0.52	0.40	0.18
	P value	**0.00**	**0.00**	**0.001**	**0.012**	0.15

Spearman's rho		1yTUG	1yStairs	1yQuad	1yPeak Hamstring	1yROM
1yr 2 min distance	R_s	-0.89	-0.69	0.66*	0.56	0.15
	P value	**0.00**	**0.00**	**0.00**	**0.00**	0.32

Table 5.7 Correlation between preoperative and 1 year KOOS score with other Patient reported outcome measures

Spearman's rho		Preop SF36 PF	Preop UCLA	Pre op AKSS	Preop EQ-5D
Preop KOOS	r_s	0.66*	0.51	0.43	0.35
	P value	**0.00**	**0.00**	**0.001**	**0.01**

Spearman's rho		1y SF-36 PF	1y UCLA	1y AKSS	1y EQ5D
1yr KOOS	r_s	0.57	0.42	0.33	0.34
	P value	**0.000**	**0.002**	**0.019**	**0.013**

Table 5.8 Correlation between KOOS and functional outcome tests

Spearman's rho		Preop 2minDist	Preop TUG	Preop stairs	PreopQuad	Preohamstring	Preop ROM
Preop KOOS	r_s	0.40	-0.41	-0.40	0.33	0.38	0.27
	P value	**0.003**	**0.002**	**0.004**	**0.091**	**0.044**	**0.049**

Table 5.9 Correlation pre-KOOS with novel functional outcome tests

Spearman's rho		Balance	Ability to Kneel	Up Slope Grad	Up Slope Speed	Down Slope Grad	DownSlope Speed	pebble difficultly	Pain Score
Pre-op KOOS	r_s	-0.02	0.39**	0.44*	0.42*	0.41	0.32	-0.44	-0.58
	P value	0.89	**0.003**	**0.02**	**0.02**	**0.03**	**0.09**	**0.02**	**0.000**

The Two minute walk test was selected as a well-validated functional test to correlate with the other functional tests using the Spearman's rank-order correlation to assess the relationship between tests both pre- and post-operatively. The strongest positive correlation was between the Two minute walk test and the TUG (r_s=-0.90, p=0.00). Pre-operative and post-operative ROM did not demonstrate a significant correlation with the Two-minute walk test (r_s =0.18, p=0.15).

Regarding the patient reported outcome measure the KOOS score was compared to the other PROMS pre-operatively and at 1 year and the strongest correlation was between the KOOS and the SF-36 pre-operatively (r_s=0.660, p <0.0005). There was a significant correlation with all patient reported outcome measures both pre- and post-operatively. When comparing the KOOS with the functional tests scores the closest correlation was with the Two minute walk test (r_s=0.40, p=0.0003). Range of motion both pre- and post-operatively did not demonstrate a significant correlation with other functional tests and correlated only weakly with the KOOS score (r_s= 0.269, p=0.049).

Comparing the KOOS score with the novel function tests, the KOOS score correlated significantly with the patients' ability to kneel (r_s =0.39, p=0.0.3) and the patients' pain score (r_s=-0.58). The gradient at which the patient felt they could walk up and down hill on the treadmill and the difficulty walking across pebbles did demonstrate a significant correlation but not as strong as the pain scores.

5.5 Discussion

There was no significant difference in the early functional outcome of KA TKA compared with conventional MA TKA, when performed on an unselected cohort of patients with end-stage non-inflammatory arthritis of the knee. There were, however, trends towards earlier functional improvement at 6 weeks for some of the outcome measures (KOOS and Peak torque of the quadriceps) in the KA group, but this was not maintained at 1 year. There were significant improvements in both the joint specific and generic outcome measures for both groups compared with the pre-operative values.

The patient-specific instrumentation had equivalent accuracy to the standard instrumentation and the number of outliers were in keeping with the findings of a recent meta-analysis on methods of alignment (Mannan et al. 2015). More detailed pre-operative imaging techniques and a better understanding of what constitutes a patient's normal alignment and flexion axis has led to the possibility of using methods of alignment other than the standard mechanical alignment. The study used a comprehensive number of both joint specific and generic health scores (KOOS, AKSS, ULCA, SF-36 and EQ-5D) to assess outcome alongside validated tests of function performed in a physiotherapy gymnasium. The theory behind this was that although labour-intensive to perform and record, these functional tests may give more subtle variations in the patient's performance pre- and post-operatively and allow more detailed functional assessment. However, despite the number of assessment tools no significant difference was demonstrated between KA and MA.

The general trend was of significant improvement 1 year post-operatively in both groups compared to pre-operatively. There was a steady improvement in the ULCA, KOOS and SF-36 scores and the TUG and Two minute walk tests during the post-operative period. This is in contrast to the quantifiably measured functions of ROM and peak torque in the hamstrings which decreased initially before improving. This could be attributed to pain relief as a consequence of the TKA resulting in an improved perception of function by the patient. The peak torque in the quadriceps and hamstrings, and the functional component of the AKSS, all showed a significant improvement in the first 3 months in the KA group compared with the mechanically aligned group. Although this suggests an improved early recovery in the KA group, there was no difference at 1 year.

The correlations between the functional tests demonstrated that range of motion is in fact a poor surrogate marker of a patients' function. This may be because once a patient can achieve a certain degree of flexion their ability to perform tasks such as walking up and down stairs is independent of their movement. In the study the average pre-operative range of motion was 106° so the majority of patients in the trial actually had reasonable movement. The correlation with other tests may have been closer if the baseline range of motion had been less.

The correlations between the KOOS score and the other PROMs were all significant. This is not surprising given that all the PROMs used have been extensively validated. It is however reassuring to know that when interpreting studies that do not use all of

the PROMs used in this study the result could be extrapolated and compared to the other outcome measures.

In terms of comparing the KOOS with some of the common functional outcome tests, again there were significant correlations. The KOOS demonstrated very strong correlation with the Two minute walk, the Timed up and go and the Timed stair walking. The Myometer measuring torque was also significantly correlated with the KOOS. It could be interpreted therefore that it is unnecessary to subject the patient and the assessor to the time consuming and potentially uncomfortable tests if a questionnaire produces the same results. That said there were subtle changes in the Myometer that a questionnaire may be unable to pick up. The reduction in peak quadriceps torque in the first 6 months post-operatively before improving to becoming better than baseline is an interesting finding. An explanation for this might be the length of time the extensor mechanism takes to recover from being violated during the medial para-patella approach. The other tests were not sensitive enough to pick up this change.

The correlation of the KOOS score to the novel functional outcome tests was also interesting. It is of note that there was a strong correlation between the KOOS and a numerical pain score. The KOOS questionnaire has a whole subsection on pain relating to certain activities. In this instance an argument could be made for reducing the length of the KOOS pain section. The patient's actual observed ability to kneel was also strongly correlated with the KOOS score. The KOOS score does have a specific question relating the degree of difficulty the patient experienced kneeling

due to their knee. The figure of 81%-85% of patients being able to kneel in the post-operative period is high but is in keeping with other studies looking specifically at kneeling after TKA (Palmer et al. 2002). Previous studies have demonstrated a discrepancy between patient perceived ability to knee and their actual ability to kneel (Schai et al. 1999). This study adds further objective evidence of what patients can expect in terms of kneeling following their TKA.

The Wii Fit™ balance board did not appear to be reliable indicator of function in terms of its poor correlation with the KOOS score. It has been demonstrated as a potential adjunct to physiotherapy following TKA (Fung et al. 2012), but on the basis of this trial, it is not a reliable measure of patient function.

The gradient at which the patients could walk up and down a slope on a treadmill as well as the ability to walk across an uneven surface did correlate significantly with the KOOS score. These tests appear to produce results in keeping with other validated tests and may be valuable in providing additional information for a subset of patients who report instability in their TKA.

The study had limitations. Small deviations from the desired alignment may have affected the outcome, although the cutting blocks were at least as accurate as the intra- and extra-medullary guides in the mechanically aligned group. It is possible that a Type II error could have occurred to the MA group.

Follow-up at 1 year has been shown to predict long-term functional outcome (Howell et al. 2013) but longer-term review is required to assess if KA will have an effect on function and survivorship. This is particularly true for the outliers in the KA group, where three patients had valgus alignment of >6°. The study was not powered to assess specific subgroups that may benefit from KA. The pre-operative deformity in the KA group ranged from 7° varus to 7° valgus, which is representative of most knees with osteoarthritis. Knees with a deformity of >10° were not included and therefore adopting KA for those with a complex deformity would require further investigation.

There were no catastrophic failures in the KA group, as may have been feared from some of the early literature on alignment (Fang et al. 2009). Theoretically trying to reproduce more naturally aligned TKAs appears to be a logical progression in an attempt to improve the outcome. However, this RCT did not disprove the null hypothesis and failed to demonstrate any discernible difference between TKAs implanted in KA or MA. Mid to longer-term follow-up is required to confirm the equivocal functional outcomes and that survival of the TKA is not compromised by kinematic relative to mechanical alignment.

Chapter 6 Effect of Kinematic Alignment on Peri-Prosthetic Bone Mineral Density, after Total Knee Arthroplasty

6.1 Introduction

One of the main concerns with KA is that it will lead to abnormal loading around the knee prosthesis, and this may in turn lead to bone collapse, particularly on the tibial side, and ultimately implant failure. Having a patient cohort with TKAs implanted in KA gave a unique opportunity to study the impact this would have on the BMD around their prostheses. The aim of this study was to look at DEXA scans in Regions Of Interest (ROI) around the knee to see what the effect of overall alignment and individual component alignment had on BMD. The hypothesis was that patients with varus tibial components would have increased BMD under the medial tibial plateau.

A number of studies have been published in the literature regarding bone loss around the femoral (Robertson et al. 1994; Van Lenthe & de Waal Malefijt 1997; Van Loon et al. 2001; Tissakht et al. 1996; Petersen et al. 1995; Mintzer et al. 1990; Seki et al. 1999; Soininvaara et al. 2004) and tibial (Bohr & Lund 1987; Lonner et al. 2001; Regnér et al. 1999; Soininvaara et al. 2004; Li & Nilsson 2000) components of TKAs and comparing the effects of cemented and cementless techniques (Abu-Rajab et al. 2006) on BMD. Computer software is now available that allows the measurement of BMD adjacent to metal implants (Robertson et al. 1994; Trevisan et al. 1998), with an average precision error of 2.2-2.9% in tibial regions of interest (Soininvaara et al. 2000).

Observations have been made in earlier studies regarding the pre-operative effect of alignment of BMD. Knees with varus alignment have been demonstrated to have higher levels of bone mineral density than those with valgus alignment (Li & Nilsson 2000). Even distribution of load across the tibia has been demonstrated to stimulate a loss of bone in knees with high levels of bone mineral density and an increase of bone in knees with low levels. No studies to date have looked specifically at the effects of post-operative kinematic alignment on the effects of BMD around the TKA prosthesis.

DEXA scanning is an approved method of measuring peri-prosthetic BMD (Kröger et al. 1996). The purpose of this study is to look at the effect of individual implant component position and overall Hip Knee Ankle (HKA) angle on BMD around the prosthesis when utilising the KA philosophy. The null hypothesis was that the post-operative alignment of the prosthesis would have no effect on the BMD surrounding the implant.

6.2 Methods

From the initial cohort study of patients who had received ShapeMatch® implants, a subgroup of 13 patients was identified between 2010 and 2012. The subgroup of patients were all post-menopausal women with unilateral osteoarthritis so that the disease free contralateral knee could be used for comparison. This group was selected because they lose bone systemically (at a particularly accelerated rate in the

2 years post menopause). As the patients had been included in the earlier study, the inclusion and exclusion criteria for the ShapeMatch® implants and the operative technique were as previously described.

Ethical approval for this study was obtained from the National Research Ethics Service Committee South West and the Royal Devon and Exeter Foundation Trust Research and Development Team (Appendix E). All patients were provided with a patient information booklet and informed consent was obtained.

All participants underwent DEXA (GE Lunar Prodigy, Bedford, MA) scans of both of their knees. An independent radiographer performed the scans. Raw data from the DEXA scans was analysed using the GE Lunar enCORE™ 2005 software version 9.30.044. All DEXA scans were performed 1.5 years post-operatively using a modified validated densitometric analysis protocol, to assess peri-prosthetic Bone Mineral Density (BMD). It was elected to perform the scan 18 months post-surgery as it is recognised that there is a loss in BMD in the post-operative period (Soininvaara et al. 2004) that then stabilises after mobility is regained (Cameron & Cameron 1987).

Reproducibility of assessing ROI with DEXA around the knee has been previously demonstrated; this study was a modification of previous techniques (Trevisan et al. 1998; Abu-Rajab et al. 2006). The DEXA protocol required the knee to be in full extension and in 15° of internal rotation for the anterior-posterior (AP) projection, and in lateral projection the knee was in 20° of flexion and neutral rotation. For the

lateral radiograph the femoral condyles had to be perfectly superimposed on one another for the scan to be accepted. Rubber supports and rice bags were used to fix the limb for both projections. For the lateral scans, the degree of knee flexion was checked with a goniometer.

On lateral scanning, there were five ROI (Figure 6.1). On AP scanning, there were four ROI (Figure 6.2). A template of the regions of interest was created so that identical regions could be superimposed onto each scan (Abu-Rajab et al. 2006).

Figure 6.1 DEXA scan showing regions of interest for the replaced knee from the lateral view. Lateral ROI 1,2,3,4 and 5 are illustrated.

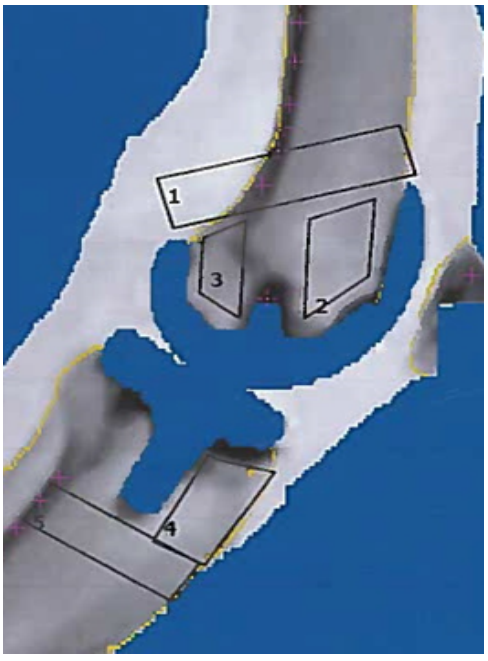
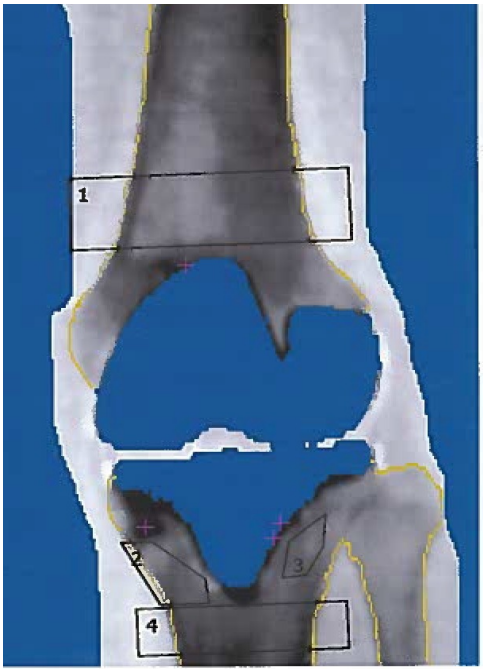


Figure 6.2 DEXA scan showing regions of interest around the prosthesis in the anterio-posterior view. ROI AP 1,2,3 and 4 are illustrated.



The contralateral knee was scanned so that the relative bone mineral density could be calculated using the equation as follows:

$$\text{Relative BMD} = 100 \times \frac{\text{(replaced knee BMD – non-replaced knee BMD)}}{\text{non-replaced knee BMD}}$$

Post-operative long leg radiographs were used to calculate the overall HKA as well as implant position relative to the Lateral Distal Femoral Angle (LDFA) and the medial Proximal Tibial Angle (mPTA). The relationship between BMD in the regions of interest and overall alignment and specific component alignment was analysed. For statistical analysis SPSS version 22 software was used (SPSS Inc.,

Chicago, Illinois) for analysing the results. The paired t-test was used with a p-value ≤0.05 defined as clinically significant.

6.3 Results

Table 6.1. illustrates the relative BMD for all the ROIs around the knee. The regions under the tibial tray in AP2 and AP3 demonstrated a trend to increased BMD in the replaced knee in comparison to the contralateral knee. The regions behind the femoral component adjacent to the pegs shown on the lateral view (Lat 2 and Lat 3) demonstrated a mean decrease in relative BMD.

Table 6.1 Relative BMD in regions of interests

Measurement outcome	ROI Relative BMD	Mean	Std. Deviation	95% Confidence Interval	
				Lower	Upper
BMD expressed as a % in comparison to the patients unreplaced knee	AP1	2.36	17.69	-8.88	13.59
	AP2	10.59	28.57	-7.57	28.74
	AP3	2.44	16.22	-7.87	12.75
	AP4	-0.19	5.45	-3.65	3.27
	Lat1	4.27	17.64	-6.94	15.48
	Lat2	-23.02	12.99	-31.28	-14.77
	Lat3	-21.98	16.83	-32.68	-11.289
	Lat4	-2.89	15.66	-12.84	7.07
	Lat5	-2.98	10.72	-9.80	3.83

The different scores were symmetrically distributed. A Wilcoxon signed-rank test (Table 6.2) determined that there was a statistically significant mean decrease in both the ROI Lateral 2 and Lateral 3 when comparing the post-operative knee to the contralateral knee (z=2.98, p=0.003 and z=-2.81, p=0.003).

Table 6.2 showing results of Wilcoxon signed-rank test comparing the replaced knee with the non-replaced knee

Measurement outcome	ROI	ShapeMatch® Knees				Non-replaced knees				P value for Wilcoxon signed-rank test
		Mean	SD	95% Conidence Interval		Mean	SD	95% Confidence Interval		
				Lower	Upper			Lower	Upper	
BMD (g/cm^2)	AP1	**0.76**	0.13	0.68	0.84	**0.76**	0.17	0.65	0.86	0.94
	AP2	**0.78**	0.13	0.69	0.86	**0.72**	0.13	0.64	0.80	0.34
	AP3	**0.84**	0.21	0.71	0.98	**0.82**	0.13	0.74	0.91	0.64
	AP4	**1.01**	0.20	0.88	1.13	**1.01**	0.18	0.89	1.12	0.90
	lat1	**1.09**	0.22	0.95	1.23	**-1.77**	14.25	-10.82	7.29	0..88
	lat2	**0.73**	0.22	0.59	0.87	**0.94**	0.16	0.83	1.04	**0.003**
	lat3	**1.22**	0.32	1.01	1.43	**1.57**	0.32	1.37	1.78	**0.003**
	lat4	**0.60**	0.12	0.52	0.67	**0.62**	0.14	0.54	0.71	0.53
	lat5	**0.75**	0.14	0.66	0.83	**0.77**	0.13	0.69	0.85	0.24

A Spearman's rank-order correlation was run to assess the relationship between overall XR alignment and relative and actual BMD in regions of interest around the prosthesis (Table 6.3). Preliminary analysis showed the relationship to be monotonic, as assessed by visual inspection of a scatterplot. There was a strong positive correlation between overall alignment and BMD in the AP2 ROI under the tibial tray. The Spearman's rank-order correlation was also run to assess the relationship between the ROIs and the MPTA and LDFA (Table 6.4). Looking specifically at the ROI AP2 and AP3 under the tibial tray there was no correlation

between the relative AP2 BMD and MPTA (r_s=-0.363 p=0.246) and there was no correlation between relative AP3 BMD and MPTA (r_s=0.243 p=0.446).

Table 6.3 showing Spearman's rank-order correlation between overall alignment and bone mineral

density in regions of interest

ROI	Relative BMD r_s and p value LDFA		Relative BMD r_s and p value MPTA	
AP1	-0.01	0.97	-0.47	0.13
AP2	-0.14	0.66	-0.36	0.25
AP3	-0.03	0.94	0.24	0.45
AP4	-0.12	0.72	-0.14	0.67
Lat 1	0.03	0.94	0.42	0.17
Lat 2	-0.27	0.40	0.09	0.79
Lat 3	0.40	0.19	0.06	0.85
Lat 4	-0.03	0.93	-0.12	0.72
Lat 5	0.06	0.85	-0.17	0.61

Table 6.4 showing Spearman's rank-order correlation comparing relative BMD in regions of interest (ROI) with the Lateral Distal Femoral Angle (LDFA) and Medial Proximal Tibial Angle (MPTA).

ROI	Relative BMD r_s and p value		Actual BMD r_s and p value	
AP1	0.57	0.05	0.13	0.69
AP2	-0.72	**0.0009**	0.65	**0.022**
AP3	0.38	0.23	0.39	0.21
AP4	-0.27	0.39	0.06	0.22
Lat 1	0.25	0.44	0.03	0.93
Lat 2	-0.21	0.52	0.11	0.74
Lat 3	0.60	**0.04**	0.45	0.15
Lat 4	0.16	0.62	0.23	0.47
Lat 5	0.15	0.64	-0.21	0.95

6.4 Discussion

This is the first study in the literature to look at BMD in the context of KA TKA. This study confirmed that there is a reduction of bone loss directly behind the femoral component of the implant, in keeping with other studies using MA. This has been attributed to stress shielding. The other significant finding from the study was that if the overall axis of the lower limb was in neutral, irrespective of the MPTA and LDFA, then the BMD under the tibial tray appeared to be evenly distributed. This is an important finding as it indicates that the natural obliquity of the joint line may be recreated in KA without causing abnormal loading under the tibial plateau.

The previous research looking at BMD around the knee has concentrated on implant fixation techniques and appears to have demonstrated higher rates of peri-prosthetic fractures in cementless implants (Thompson et al. 2001). Less work has looked at the effects of alignment on BMD and no previous studies have researched KA on BMD. The distal femur is the area most susceptible to stress shielding and therefore may result in a decrease in BMD, this has been demonstrated by finite element analysis (Van Lenthe & de Waal Malefijt 1997; Tissakht et al. 1996). This study demonstrated a relative 21% and 23% mean loss in BMD in comparison to the contralateral knee in ROIs Lateral 2 and 3 respectively, which is comparable to the amount of bone loss behind the anterior flange of the femoral component in previous studies (22%- 36%) (Van Loon et al. 2001; Petersen et al. 1995). The decrease in BMD behind the femoral prosthesis was found to be significant in comparison to the contralateral side p=0.003 for both ROI Lateral 2 and 3.

When examining the tibial component ROIs AP2 and AP3 demonstrated a mean increase in bone mineral density at 18 months post-operatively of 10.6% and 2.4% respectively. This is in contrast to Regner et al. (Regnér et al. 1999) who reported a decrease in BMD in the medial tibial condyle 5 years post-operatively. There was a significant negative correlation with overall alignment and relative (r_s=-0.72 p=0.009) and actual (r_s=-0.65 p=0.22) BMD in the AP2 region under the medial tibial condyle. This suggests that the bone does indeed respond to alterations in loading in this region, with increased BMD in overall varus alignment and decrease in BMD in overall valgus alignment. There was an apparent positive correlation in relative BMD and overall alignment in the lateral 3 ROI (r_s=0.60 p=0.04). This

would suggest that the more valgus the knee the greater the BMD behind the femoral pegs of the implant, even if the overall trend was for a loss of BMD behind the femoral pegs. This is interesting and might suggest that by recreating the natural alignment of valgus knees, it may have a protective effect against osteoporosis behind the femoral component.

The results suggest that there was no correlation between MPTA and LDFA taken in isolation with changes in BMD. This is of importance in the context of KA. For example, if the tibia was placed in 3° of varus and then balanced by a femur placed in 3° of valgus, then there was no overall change in BMD around the tibial component of the prosthesis. This is reassuring and would suggest that the natural obliquity of the joint line can be recreated without causing abnormal loading under the tibia. On the other hand, there was a correlation between overall alignment and changes in BMD, suggesting that if the knee had an overall varus alignment this did produce an increase in BMD under the medial aspect of the tibial plateau. This could be of concern if the increase in BMD is a precursor for potential tibial collapse. This point leads back to the question of whether deviation from the mechanical axis could lead to failure, and as discussed in the literature review, the evidence for this is now weak (Bonner et al. 2011). Long-term follow-up of this set of patients is therefore imperative to see if alignment will affect implant survivorship.

The results from this study are in keeping with other studies in demonstrating that the majority of bone loss occurs behind the femoral pegs. With a mean of 23% and a maximum bone loss of 49% in this region, it is slightly less than the maximum bone

loss of 74% reported in the Abu-Rajab et al study (Abu-Rajab et al. 2006). It could be speculated that the kinematic alignment produces more natural loading that in turn prevents stress shielding.

By specifically selecting post-menopausal women with a contralateral knee with no osteoarthritic changes, direct comparisons with relative BMD should have provided accurate data. The weakness from the study is that by selecting this specific cohort the total number of patients was small. The study provides evidence that the overall alignment of the knee, as opposed to the individual components, is what is important in determining changes in BMD around the prosthesis.

Chapter 7 Conclusion and Future Perspectives in Total Knee Arthroplasty

The aim of this thesis was to assess a new alignment technique and philosophy in TKA. A systematic and stepwise approach has been applied to the research. With the introduction of any new technique or device in orthopaedics and in medicine in general, the primary responsibility has to be towards ensuring the safety and best interests of the patients.

For this body of research the use of the computer software to predict areas of chondral defects on the tibia and femur from MRI scans in OA was a new technique, as was the software to predict alignment of the lower limb in the pre-arthritic state and the patient specific instrumentation and cutting blocks. As such it was imperative that the new technology was introduced in a controlled fashion. The initial proof of concept case series, followed by the feasibility study and then the RCT, was a responsible way of testing the technology.

The proof of concept study demonstrated that there appeared to be a good correlation between the proposed alignment for each individual patient and what was being achieved intra-operatively. This was in keeping with the previous cadaveric study by Clark (Clark et al. 2013). The feasibility study provided evidence that it would be possible to run an RCT. The early functional results were encouraging in comparison to what was the standard prosthesis being used in the department at the time.

The feasibility study appeared to demonstrate improved outcomes with regard to the WOMAC scores and the OKS in the KA group of patients in comparison to the MA group. This result was not replicated in the RCT. There are a number of explanations for this. The feasibility study was a prospective comparative study, and so by definition would represent Level II evidence. The patients were not randomised in the feasibility study and even though the patients were matched in terms of baseline characteristics there was selection bias. Motivation could also have been higher in the KA group given the knowledge they were trialing a new implant, which could have lead to improved results.

The alternative explanation for the improved results in the feasibility study is that there was a genuine difference in the two groups, but it was not the alignment of the implant that led to the improved outcome, but rather the subtle differences in implant design. The Scorpio® is undoubtedly a bulkier implant and the single radius of curvature differs slightly from that of the Triathlon®. The Triathlon® TKA has been demonstrated to produce patient satisfaction of 88% when implanted in mechanical alignment (Scott et al. 2015), and it is possible it outperformed its predecessor.

The results from the RCT demonstrated that there was no difference in outcome between the two patient groups. The RCT represents Level I evidence and the design of this study should have been more robust to protect against bias than the feasibility study. That said, if the standard deviation for the power equation used the 6 month results of the WOMAC score from Chapter 4 then the study would have been underpowered.

It could be that the improved results of the Triathlon® implant, led to a ceiling effect and it was not possible to detect, even with the extensive array of outcome tools that were used, any discernable difference between the two patient groups. The idea of using such a variety of outcome measures was to try and identify subtle differences in patient outcome. It is also true that small deviations in the desired alignment may have affected outcome, and this could have affected both groups of patients. If the MA group had had their prostheses implanted closer to their natural alignment their outcome may have been improved. Evidence from Vanlommel (Vanlommel et al. 2013) suggested that under correction can improve outcome. Equally deviation in the KA group from the desired alignment could have affected outcome. The total number of patients in the RCT was relatively small, so outliers would have had a greater effect on overall results than if there had been a larger study size.

The correlation between commonly used outcome measures and the physical function tests was reassuring. The KOOS correlated strongly with the other PROMS, but more importantly with the objective functional tests such as the Two-minute walk and the Timed get up and go test. The study did therefore provide evidence that the time-consuming and labour-intensive functional tests are largely unnecessary for basic patient follow-up. It was interesting that range of motion correlated relatively poorly with other functional tests. An explanation for this may have been that range of motion was reasonable in the majority of the pre-operative patients, since this in itself is a predictor of post-operative range of motion, then there was a ceiling effect once patients could flex beyond a certain amount.

The DEXA study correlating bone mineral density with alignment yielded interesting results. The fact that overall alignment rather than individual component alignment affected bone mineral density under the tibial plateau has clinical implications in the future. The study should provide reassurance to surgeons who are apprehensive about KA that, provided the overall alignment remains within 3° of MA, then the bone under the tibial plate does not appear to be abnormally loaded. Of course with follow-up only to 18 months, predictions on longevity and survivorship cannot be made.

The Otismed® ShapeMatch® technology (Stryker Corporation, Mahwah, NJ, USA) received its FDA approval in 2011, although the ShapeMatch® cutting guides were formally recalled by the FDA with a Class I recall in 2013. The recall was over concerns by some surgeons in America that the manufactured cutting guides were not meeting the pre-operative planning parameters entered via the web application. As such no further new research into Otismed® ShapeMatch® cutting guides aiming to implant TKAs in KA has been undertaken. However better precision tools in the form of CN and robotic technology, instead of PSI, has led to new techniques in alignment being explored.

There has been interest in exploring KA but within certain defined limits. The adjusted MA technique is an adaptation of conventional MA but with the goal to under-correct the constitutional fontal deformity (varus or valgus) to a maximum of 3°. The aim of this technique is to keep the tibial component in MA, theoretically

reducing the risk of tibial collapse, but adjusting the position of the femoral component (De Muylder et al. 2015).

Similar to the adjusted MA technique some surgeons have used restricted KA in patients with substantial coronal limb deformity or joint line obliquity. CN is used to assess limb and femoral and tibial components frontal alignment. Frontal limb deformity of (≤3°) and a MPTA and LDFA of 5° obliquity is deemed in the safe zone (Hutt et al. 2016). The CN can guide the surgeon to make the appropriate obliquity and depth of cut.

Stephen Howell, from the University of California, who was one of the first to use the KA technique, has now developed a manual instrumentation technique to achieve KA. A caliper is used to measure and adjust the thickness of the distal femoral, posterior femoral, and proximal tibial resections (MD et al. 2018). This technique relies on the surgeon being able to correctly predict the width of the cartilage defect, and must therefore be susceptible to a degree of human error.

To date there is little research into the use of robot-assisted surgery in TKAs. There has been one early report in the literature of robot-assisted TKA using the kinematic axis, published online in Feb 2018 in Orthopaedic Proceedings. 50 knees were evaluated using the ROBODOC (ISS Inc., CA, USA) and the ORTHODOC (ISS Inc., CA, USA) planning computer, with 6 weeks follow-up. The study did not report on the accuracy of the implant position in comparison to the pre-operative plans. Robot surgery represents the latest technology available to assist the surgeon. It is

too early to say if it will improve patient outcome in TKA but abundant research is likely to be published in this field over the next few years.

The demographics of patients receiving knee replacements are changing with both older and younger patients being considered for surgery. In the UK the average age of patients undertaking TKA is 70 years of which 58% are female (NJR 2017). Patients at the extreme ends of the age spectrum present different surgical problems.

TKA has historically been avoided in the younger patient because of concerns over the longevity of implant survival and the technical difficulties with revision surgery. This is changing to an extent, as now the survivorship of most TKAs is in excess of 90% at 15 years, and techniques of revision surgery are greatly improving. The younger patient does tend to have greater functional demands of the implant and greater expectations of what is functionally achievable following knee arthroplasty. This means that there is an ongoing need to improve the wear characteristics of the prosthesis and the knee kinematics to try and restore function.

The current perception is that certain activities are difficult following knee TKA. With regards to function, flexion has been improved with the modern prosthetic knee designs. Pre-operative range of motion remains the most accurate predictor of post-operative range of motion. Patients frequently describe difficulty with kneeling, squatting, walking on a slope and high impact activities. One of the goals for future knee arthroplasty is to improve the performance of these types of tasks without

compromising the survivorship of the implant.

Improving the kinematics of the knee replacement may lead to greater risk of wear, loosening and peri-prosthetic fracture. More active patients will increase the cyclic load. It has been demonstrated in hip arthroplasty that there is a correlation between higher walking speeds and wear (Schmalzried et al. 2000). Previously patients have been discouraged from participating in high impact sports to prevent aseptic loosening (Ritter & Meding 1987; Bonnin et al. 2009; Hartford 2003).

The patient population is also getting older and the older group of patients presents a different set of problems. Wear of the implant is perhaps not so great a concern; rather the physiological demands that the operation places on the body. Future developments for this cohort therefore need to involve reducing the physiological stress. Techniques that involve reducing operating time, blood loss and embolic load, are potentially beneficial.

The past decade has seen an increase in obesity rates for patients having primary knee procedures. This figure has increased from an average of 29.2 to 30.6 over the past 6 years along with a steady increase in the number of patients within the BMI range 30 to 39 and a decrease of patients with BMI less than 30. This trend means that the average knee replacement patient is now clinically obese. The obese patient presents yet another set of problems. Technically the surgery is often demanding

because of difficulty obtaining adequate access. Obese patients have a higher incidence of co-morbidities such as diabetes, predisposing them to infection. The increased weight puts greater stress through the prosthesis.

In conclusion the demand for TKA is set to increase in the foreseeable future. Analysis of data for England and Wales suggest that by 2030, the volume of primary and revision TKAs will have increased by 117% and 332% respectively, between 2012 and 2030 (Patel et al. 2015). This will have a massive financial impact on the NHS and needs to be qualified in in terms of patient outcome. Patient dissatisfaction following TKA appears to range from between 11-19% (Bourne et al. 2010; Baker et al. 2007), highlighting the need for continued innovation in the discipline of knee surgery to try and improve patients functional outcomes.

Trying to reproduce more natural knee kinematics in TKA seems a logical target for engineers and surgeons as a way of aiming to improve patient function and outcome following surgery. The research undertaken in this thesis failed to rejected the null hypothesis and demonstrated that current kinematic technology has not outperformed traditional MA techniques. That said it has already been demonstrated that implanting TKAs in mechanical alignment with greater accuracy does not improve patient outcome (Y et al. 2008). The 5 year results from the RCT will be available within the next year, it will be of critical importance to publish these and see if the KA group have the same implant survivorship as the MA group. I plan to construct a RCT comparing TKAs implanted in KA versus MA with the use of robotic surgery.

The hypothesis will be that the robot in conjunction with CT planning will be more accurate in predicting and executing the correct implant alignment, and this in turn will lead to improve patient outcomes following TKAs.

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Appendices

Appendix A: Published papers

Waterson HB, Clement ND, Eyres KS, Mandalia VI, Toms AD. The early outcome of kinematic versus mechanical alignment in total knee arthroplasty: a prospective randomised control trial. Bone Joint J. 2016 Oct;98-B(10):1360-1368.

Waterson HB, Philips JRA, Mandalia VI, Toms AD.Thou shalt not varus: still applicable in total knee arthroplasty. Bone and Joint 360. Published 3 June 2014

■ KNEE

The early outcome of kinematic *versus* mechanical alignment in total knee arthroplasty

A PROSPECTIVE RANDOMISED CONTROL TRIAL

H. B. Waterson,
N. D. Clement,
K. S. Eyres,
V. I. Mandalia,
A. D. Toms

From Exeter Knee Reconstruction Unit, Princess Elizabeth Orthopaedic Centre, Royal Devon & Exeter Hospital, Exeter, United Kingdom

■ H. B. Waterson, FRCS (Tr&Orth), Specialty Trainee Trauma and Orthopaedics
■ N. D. Clement, PhD, FRCS (Tr&Orth), Specialty Trainee Trauma and Orthopaedics Royal Infirmary of Edinburgh, Little France Crescent, EH16 4SA, UK.

■ K. S. Eyres, MD, FRCS (Tr&Orth), Consultant Orthopaedic Surgeon, Exeter Knee Reconstruction Unit
■ V. I. Mandalia, FRCS (Tr&Orth), Consultant Orthopaedic Surgeon, Exeter Knee Reconstruction Unit
■ A. D. Toms, MSc, FRCS (Tr&Orth), Consultant Orthopaedic Surgeon, Exeter Knee Reconstruction Unit Princess Elizabeth Orthopaedic Centre, Royal Devon & Exeter Hospital, Exeter, UK.

Correspondence should be sent to Mr H. B. Waterson; e-mail: benwaterson@nhs.net

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Aims
Our aim was to compare kinematic with mechanical alignment in total knee arthroplasty (TKA).

Patients and Methods
We performed a prospective blinded randomised controlled trial to compare the functional outcome of patients undergoing TKA in mechanical alignment (MA) with those in kinematic alignment (KA). A total of 71 patients undergoing TKA were randomised to either kinematic (n = 36) or mechanical alignment (n = 35). Pre- and post-operative hip-knee-ankle radiographs were analysed. The knee injury and osteoarthritis outcome score (KOOS), American Knee Society Score, Short Form-36, Euro-Qol (EQ-5D), range of movement (ROM), two minute walk, and timed up and go tests were assessed pre-operatively and at six weeks, three and six months and one year post-operatively.

Results
A total of 78% of the kinematically aligned group (28 patients) and 77% of the mechanically aligned group (27 patients) were within 3° of their pre-operative plan. There were no statistically significant differences in the mean KOOS (difference 1.3, 95% confidence interval (CI) -9.4 to 12.1, p = 0.80), EQ-5D (difference 0.8, 95% CI -7.9 to 9.6, p = 0.84), ROM (difference 0.1, 95% CI -6.0 to 6.1, p = 0.99), two minute distance tolerance (difference 20.0, 95% CI -52.8 to 92.8, p = 0.58), or timed up and go (difference 0.78, 95% CI -2.3 to 3.9, p = 0.62) between the groups at one year.

Conclusion
Kinematically aligned TKAs appear to have comparable short-term results to mechanically aligned TKAs with no significant differences in function one year post-operatively. Further research is required to see if any theoretical long-term functional benefits of kinematic alignment are realised or if there are any potential effects on implant survival.

Cite this article: *Bone Joint J* 2016;98-B:1360–8.

The number of total knee arthroplasties (TKAs) performed in the United Kingdom has been increasing each year with more than 90 000 being recorded by the National Joint Registry of England, Wales and Northern Ireland in 2013.[1] The ten-year revision risk for cemented, unconstrained fixed bearing TKA is just over 3%.[1] TKA is now a more common procedure than total hip arthroplasty (THA) but satisfaction following TKA remains inferior.[2-5] The cause of this dissatisfaction is not clear. The knee is a complex joint involving movement in 6° of freedom and errors in alignment of the components can lead to alteration in the kinematics of the knee, which potentially compromise the outcome.

The concept of mechanical alignment was developed as a compromise,[6] in an attempt to improve survivorship of the early rudimentary designs of TKA. Distribution of the load evenly across the components was thought to confer mechanical advantage, ignoring the patient's natural alignment. Until now, this compromise has not been revisited. Due to the limitations in design and accurate analysis of alignment, the success of a TKA has historically been measured by the survivorship of the components, largely determined by their alignment in the coronal plane. Surgeons have had to rely on radiographs when analysing alignment. A disproportionate amount of research has therefore focused on coronal alignment and the relationship the components have to the mechanical axis. Deviation from neutral overall alignment in the coronal plane has previously been thought to contribute to reduced

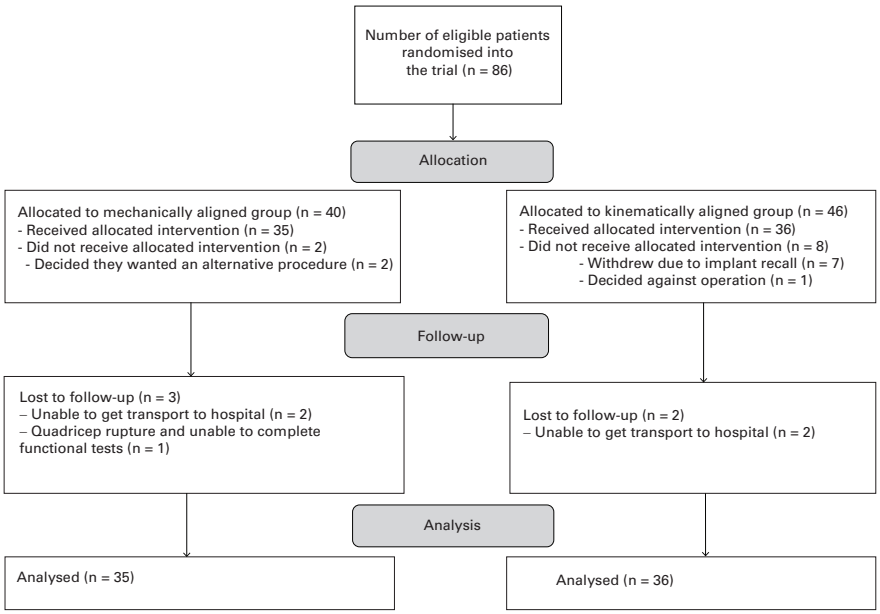

Fig. 1

Flow Diagram of Consolidated Standards of Reporting Trials recruitment and follow-up.

survivorship.[7-10] Recent technology has focused on ways of reproducing neutral alignment. Computer navigation was one such innovation that improved the accuracy of alignment,[11,12] but this has not been translated into improvement in functional outcome or satisfaction.[13-15] Current data from national joint registries shows that implant survival is no longer comparable to that of the early designs of TKA,[1] and recent authors have suggested that deviation from neutral alignment does not have the detrimental effect on survivorship as previously thought.[13,16,17]

Improvements in imaging have led to an increased understanding and appreciation of alignment in TKA by being able to assess the joint in three dimensions. The use of CT scans has become the reference standard when measuring alignment.[18] The concept of what constitutes normal alignment has been reconsidered. It has been shown that 32% of men and 17% of women have constitutional varus knees.[19] The use of more detailed imaging has called into question established reference landmarks regarding alignment. The studies by Eckhoff et al[20-23] concluded that the axis of the leg is not straight and the true axis of flexion and extension does not correspond with the epicondylar axis. Coughlin et al[24] established a direct correlation between the axis of flexion and extension and the axis of the patella. The use of both MRI and CT scans has also lead to the development of patient-specific instrumentation. The implant manufacturers' bespoke computer software is used to create a 3D reconstruction of the patient's knee from which custom made cutting blocks are produced to assist the surgeon in making the desired femoral and tibial cuts.

The concept of implanting the components in such a way as to recreate the alignment in the pre-arthritic state has been termed natural or kinematic alignment. This is one of the first independent studies from Europe evaluating whether kinematic alignment results in improved early functional outcome when compared with traditional mechanical alignment. The aim of this randomised controlled trial was to compare the early (one year) functional outcome for kinematically aligned TKA with that of mechanically aligned TKA using a wide range of patient reported outcome measures and functional assessment tasks. The null hypothesis was that kinematically aligned TKA was not associated with superior functional outcome when compared with mechanically aligned TKA.

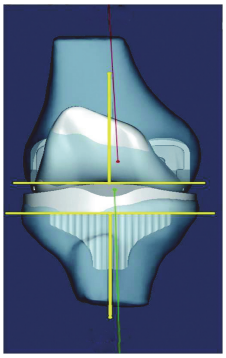

Fig. 2

Pre-operative MRI plan, with proposed kinematic alignment in relation to mechanical axis.

Patients and Methods

Patients were recruited from the waiting list of three consultant orthopaedic surgeons (ADT, VIM, KSE) between December 2011 and April 2013. The inclusion criteria were age between 18 to 85 years with a diagnosis of degenerative osteoarthritis. Patients were excluded if they had: a varus or valgus deformity > 10º or a flexion contracture of > 20º; if they had undergone any orthopaedic procedure to the lower limbs within the past year; a history of unsuccessful contralateral partial or TKA; any implanted prosthesis that would interfere with MRI scans; a neuromuscular or neurosensory deficiency; inflammatory arthritis. In addition patients who suffered a complication which might influence the functional outcome, such as deep infection, fracture or dysfunction of the extensor mechanism were excluded from the assessment of function one year post-operatively.

A flow diagram of the patients in the study, according to the CONSORT Guidelines is shown in Figure 1. A total of 86 patients fulfilled the criteria and were recruited to the study. Of these 71 (83%) underwent surgery and were followed up for one year. Seven patients in the kinematically aligned group were recruited but were withdrawn due to a medical device class 1 recall in April 2013. A total of five patients were lost to follow-up. One patient decided not to have an operation, one patient opted for a patellofemoral replacement and one decided they wanted a kinematically aligned TKA, and so withdrew. One patient sustained a post-operative rupture of the extensor mechanism and was withdrawn from functional assessment.

The patients who entered the trial were given a booklet outlining the details of the surgery and follow-up requirements. A true random number generator program was used and cards displaying the numbers 1 (for kinematically aligned) or 2 (for mechanically aligned) were placed in sealed envelopes. Following signed consent, the patients were allocated an envelope that was opened in the sequence ascribed by the generator. All patients were reviewed at a pre-operative clinic and at six weeks, three and six months and one year post-operatively by a research physiotherapist, (RS) who was blinded to the patients' treatment modality.

Function was assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS),[25] the University of California at Los Angeles activity score (UCLA),[26] the forgotten knee score,[27] the EuroQol EQ-5D[28] and Short Form (SF)-36 health and quality of life scores,[29], which were collected at each visit. A physiotherapist (RS) blinded to the form of TKA that was used, assessed the timed get up go (TUG),[30] two minute walk,[31] timed up and down stairs,[32] peak quadriceps and hamstring torque on a digital myometre (MIE Medical Research Ltd., Leeds, United Kingdom) as well as completing the American Knee Society score (AKSS)[33] and measuring range of movement (ROM) with a goniometer. Coronal alignment on the pre- and post-operative HKA radiographs was analysed by the authors.

Patients in the kinematically aligned group had MRI scans pre-operatively. The surgeon was then sent a surgical plan with the proposed alignment specific for each patient according to their own kinematic alignment (Fig. 2). No corrections were made to the plan before the patient-specific cutting blocks were made. The TKAs were performed either with the patient-specific cutting blocks to achieve kinematic alignment or with standard extra and intramedullary instrumentation to achieve mechanical alignment. A medial parapatellar approach without the use of a tourniquet was used. The cemented Stryker Triathlon (Stryker Navigation, Kalamazoo, Michigan), cruciate retaining knee system with patellar resurfacing was used in both groups. The post-operative protocol was identical for both groups. The operations were performed by one of three consultant orthopaedic surgeons (ADT, VIM, KSE) who were familiar with both techniques. Ethical approval for this study was obtained from the National Research Ethics Service Committee Cambridge East.

Statistical analysis. The study was powered to demonstrate a 19 point difference in the KOOS score which has been defined as the minimal clinical important change in the score.[34] Assuming a 15 point standard deviation in the score[35] a size effect of 0.66 was used to power the study. Using a one tailed analysis (assuming superior results with the kinematically aligned group) and an alpha of 0.05 with a power of 0.80, 60 patients (30 in each arm) were required. Assuming a 15% loss to follow-up at one year, a total of 70 patients needed to be recruited. The functional assessment and patient reported outcome scores are presented as means with standard deviations (SD), with 95% confidence intervals (CI). Differences between the groups were analysed using unpaired *t*-tests for improvement at

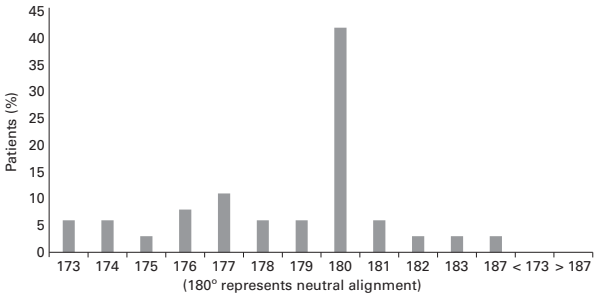

Fig. 3

Graph illustrating overall MRI alignment plans for the kinematically aligned group.

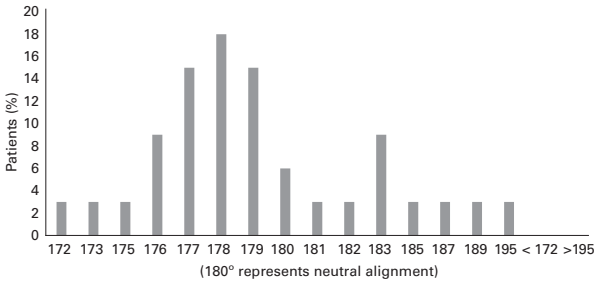

Fig. 4

Graph illustrating the distribution of post-operative overall alignment in the kinematically aligned group.

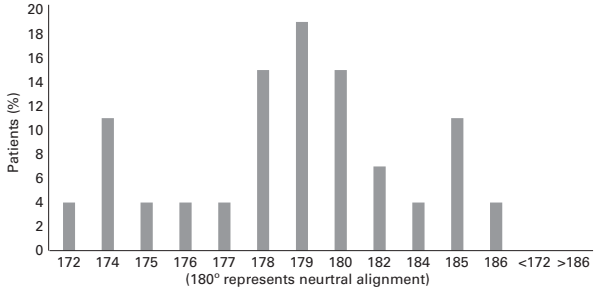

Fig. 5

Graph illustrating the distribution of post-operative overall alignment in the mechanically aligned group.

four time points after surgery. SPSS version 17 software was used (SPSS Inc., Chicago, Illinois) for analysing the results. A p-value ≤ 0.05 was defined as clinically significant.

Results

The pre-operative MRI alignment plans for the kinematically aligned group ranged from 7° of varus to 7° of valgus

Table I. Post-operative American Knee Society Score and Knee Injury and Osteoarthritis Outcome Score

	KA		MA			95% CI		
PROM	**Mean**	**SD**	**Mean**	**SD**	**Mean difference**	**Lower**	**Upper**	**p-value***
AKSS								
6 wks	65.7	13.1	59.0	9.2	6.7	0.1	13.2	0.05
3 mths	78.4	21.1	69.1	17.5	9.3	-1.6	20.1	0.09
6 mths	79.8	21.3	77.0	19.8	2.8	-8.5	14.0	0.62
1 yr	83.5	21.4	87.8	15.9	-4.3	-14.9	6.3	0.42
KOOS								
6 wks	59.0	15.0	59.0	15.7	0.0	-8.8	8.9	0.99
3 mths	74.3	13.2	69.8	16.0	4.5	-3.9	12.9	0.29
6 mths	74.7	20.7	70.7	16.3	4.1	-5.7	13.9	0.41
1 yr	77.7	20.0	76.4	19.0	1.3	-9.4	12.1	0.80

* Unpaired *t*-test
KA, kinematically aligned; MA, mechanically aligned; PROM, patient-reported outcome measure; SD, standard deviation; CI, confidence interval

Table II. Post-operative University of California, Los Angeles activity score, Short Form-36 and EuroQol-5D scores

	KA		MA			95% CI		
PROM	**Mean**	**SD**	**Mean**	**SD**	**Mean difference**	**Lower**	**Upper**	**p-value***
UCLA								
6 wks	4.0	1.8	4.2	1.2	-0.2	-1.0	0.7	0.67
3 mths	5.3	1.3	4.8	1.7	0.5	-0.5	1.4	0.32
6 mths	5.8	1.7	5.5	1.7	0.3	-0.6	1.2	0.54
1 yr	5.7	1.9	5.6	1.6	0.1	-0.9	1.1	0.84
SF-36 Physical Function								
6 wks	51.0	22.7	48.8	21.0	2.2	-11.0	15.4	0.74
3 mths	70.0	20.7	62.8	22.0	7.2	-5.2	19.6	0.25
6 months	73.8	24.3	58.8	27.6	15.1	0.9	29.2	0.04
1 yr	73.8	24.0	68.5	24.8	5.3	-8.6	19.2	0.45
EQ-5D								
6 wks	52.5	39.0	56.8	34.6	-4.3	-22.3	13.7	0.63
3 mths	61.4	41.5	65.5	30.5	-4.2	-22.2	13.9	0.65
6 mths	69.3	30.9	71.7	26.0	-2.4	-16.7	11.8	0.73
1 yr	79.5	12.9	78.6	19.0	0.9	-7.9	9.6	0.84

* Unpaired *t*-test
KA, kinematically aligned; MA, mechanically aligned; PROM, patient-reported outcome measure; SD, standard deviation; CI, confidence interval

with 78% (28 patients) within 3° of neutral overall alignment (Fig. 3). The mean lateral distal femoral angle (LDFA) in the pre-operative plan for the kinetically aligned group was 88° (83°to 92°) and the mean medial proximal tibial angle (MPTA) was 87° (80° to 93°). A total of 28 patients (78%) (Fig. 4) in the kinematically aligned group and 27 (77%) (Fig. 5) in the mechanically aligned group had their post-operative alignment within 3° of the MRI plan or neutral overall alignment respectively.

The outcome scores are shown in Tables I and II. There was a greater improvement in the mean AKSS in the kinematically aligned group at six weeks when compared with the mechanically aligned group ($p = 0.05$), but at one year there was no significant difference ($p = 0.42$). There was no significant difference in the mean KOOS, UCLA and EQ-5D scores between the two groups, at any time post-operatively. There was a slight improvement in the mean physical component of the SF-36 in the kinematically aligned group compared with the mechanically aligned group, six months post-operatively ($p = 0.04$), but the difference was not significant at one year ($p = 0.45$).

The results of the physical function tests showed a similar trend and are shown in Table III. There was no significant difference in the TUG test, the two minute walking distance test and the timed up and down stairs test at any stage post-operatively between the two groups. The measurements of peak torque in the quadriceps were significantly better in the kinematically aligned group at six weeks and three months ($p = 0.003$ and $p = 0.02$, respectively) but were not significantly different one year post-operatively. The peak torque in the hamstrings was weaker at six weeks, three months and six months post-operatively in both

Table III. Results of post-operative physical function tests

	KA		MA			95% CI		
Functional test	**Mean**	**SD**	**Mean**	**SD**	**Mean difference**	**Lower**	**Upper**	**p-value***
TUG								
6 wks	10.9	5.2	12.3	5.0	-1.4	-4.3	1.5	0.35
3 mths	8.5	2.7	9.8	3.2	-1.3	-3.0	0.3	0.11
6 mths	8.9	3.1	10.2	5.0	-1.3	-3.6	1.1	0.29
1 yr	9.8	7.6	9.1	2.8	0.8	-2.3	3.9	0.62
2 minute walk								
6 wks	112.1	35.7	96.2	29.9	15.9	-2.8	34.5	0.09
3 mths	137.0	33.5	111.9	30.7	25.0	7.5	42.6	0.01
6 mths	131.4	52.1	112.4	37.6	19.0	-4.8	42.8	0.12
1 yr	137.4	50.5	157.4	181.6	-20.0	-92.8	52.8	0.58
Timed stairs								
6 wks	22.5	13.2	21.6	10.4	0.9	-5.8	7.6	0.79
3 mths	14.2	5.8	17.2	8.6	-3.1	-7.3	1.1	0.15
6 mths	16.1	9.6	19.5	17.8	-3.4	-11.3	4.5	0.39
1 yr	13.8	10.5	16.3	9.1	-2.4	-7.8	2.9	0.37
Peak quadricep torque								
6 wks	65.8	23.0	43.3	19.0	22.5	8.4	36.7	0.01
3 mths	67.3	26.6	51.2	23.7	16.1	2.2	30.1	0.02
6 mths	74.5	35.4	58.0	26.2	16.6	-0.6	33.8	0.06
1 yr	80.6	33.6	69.9	27.4	10.7	-8.2	29.6	0.26
Peak hamstring torque								
6 wks	31.4	13.7	25.3	13.3	6.1	-3.2	15.4	0.19
3 mths	33.4	12.0	26.0	10.3	7.4	1.3	13.5	0.02
6 mths	36.8	27.2	30.1	12.2	6.7	-4.8	18.1	0.25
1 yr	40.5	18.0	33.5	13.9	7.0	-2.7	16.8	0.15
Range of movement								
6 wks	104.0	14.9	100.8	24.1	3.2	-8.9	15.3	0.60
3 mths	111.7	13.3	110.3	14.1	1.4	-6.4	9.2	0.72
6 mths	116.9	9.7	116.8	9.3	0.1	-5.1	5.3	0.97
1 yr	118.5	12.0	118.4	9.4	0.1	-6.1	6.2	0.98

KA, kinematically aligned; MA, mechanically aligned; SD, standard deviation; TUG, timed up-and-go; CI, confidence interval

groups and only exceeded the pre-operative value at one year. There was no significant difference in the mean ROM, ability to kneel or walk across an uneven surface at any stage between the two groups.

A subgroup analysis was performed comparing those in the two groups whose post-operative radiographs were within 3° of their plan (Table IV). The mean peak torque in the hamstrings was significantly greater at one year in the kinematically aligned group ($p = 0.04$). There was a trend towards the patients in the kinematically aligned group having forgotten they had a TKA although this did not reach significance (77% *versus* 45% ($p = 0.10$, 95% CI 0.8 to 8.2)). Further assessment comparing the functional outcome at one year of patients within 3° of planned alignment and those outside 3° in the kinematically aligned group is shown in Table V. Again peak torque in the hamstrings was significantly greater at one year in the group that was within 3° of the planned kinematic alignment.

Discussion

We found no significant difference in the early functional outcome of kinematically aligned TKA compared with conventional mechanically aligned TKA, when performed on an unselected cohort of patients with end-stage non-inflammatory arthritis of the knee. There were, however, trends towards earlier functional improvement at six weeks for some of the outcome measures (KOOS and peak torque of the quadriceps) in the kinematically aligned group, but this was not maintained at one year. There were significant improvements in both the joint specific and generic outcome measures for both groups compared with the pre-operative values.

Many authors have correlated outcome with alignment after TKA; since the advent of computer navigation and subsequently patient-specific instrumentation, the ability to introduce the components accurately has improved.[11,12] The accuracy of mechanical alignment, however, has not

Table IV. Comparison of functional assessments measured at one year for patients within 3° of planned alignment, comparing kinematic alignment (KA) with mechanical alignment (MA) groups

		Planned KA (n = 26)		Planned MA (n = 21)			95% CI		
Functional assessment		Mean	SD	Mean	SD	Difference	Lower	Upper	p-value
UCLA		6.0	1.9	5.6	1.6	0.4	-0.6	1.4	0.42
KOOS		79.3	17.0	76.4	19.0	2.9	-7.8	13.7	0.58
Function score		87.1	22.4	87.8	15.9	-0.7	-12.4	10.9	0.90
PROM range		120.0	9.5	118.4	9.4	1.6	-4.3	7.5	0.59
EQ-5D-HS		81.0	12.6	78.6	19.0	2.4	-7.3	12.0	0.62
Pain score		1.6	1.8	1.9	1.1	-0.2	-2.0	1.5	0.78
TUG time		9.4	8.3	9.1	2.8	0.3	-3.1	3.8	0.85
2 min distance		146.2	51.7	157.4	181.6	-11.2	-93.6	71.2	0.79
Peak Tq quads		88.1	33.9	69.9	27.4	18.2	-1.8	38.2	0.07
Peak Tq hams		44.3	18.0	33.5	13.9	10.9	0.6	21.1	0.04
SF-36	PF	72.4	23.3	75.8	23.2	-3.4	-18.3	11.5	0.65
	RP	70.2	27.9	71.1	21.5	-0.8	-16.9	15.3	0.92
	RE	82.5	24.1	85.5	20.6	-3.0	-17.4	11.4	0.68
	SF	46.4	10.6	45.8	7.4	0.6	-5.4	6.6	0.84
	MH	62.6	11.6	65.8	8.4	-3.2	-9.7	3.4	0.33
	EV	49.7	13.3	51.6	12.3	-1.9	-10.2	6.3	0.64
	Pain	39.0	33.3	26.5	21.6	12.5	-7.1	32.1	0.20
	GH	53.1	12.3	49.5	15.2	3.6	-5.2	12.4	0.41
	CH	28.6	25.4	33.3	25.7	-4.8	-21.4	11.9	0.56

KA, kinematically aligned; MA, mechanically aligned; CI, confidence interval; SD, standard deviation; UCLA, University of California, Los Angeles; KOOS, Knee Injury And Osteoarthritis Outcome Score; PROM, patient-reported outcome measure; EQ, EuroQol; TUG, timed up-and-go; Tq, torque; quads, quadriceps; hams, hamstrings; SF, short-form; PF, Physical Health; RP, Role-Physical; RE, Role-Emotional; SF, Social Functional; MH, Mental Health; EV, Emotional Vitality; GH, General Health; CH, Change Health

been associated with improved outcome.[13-15] In this study the patient-specific instrumentation had equivalent accuracy to the standard instrumentation and the number of outliers were in keeping with the findings of a recent meta-analysis on methods of alignment.[36] More detailed pre-operative imaging techniques and a better understanding of what constitutes a patient's normal alignment and flexion axis has led to the possibility of using methods of alignment other than the standard mechanical alignment. The expectation of a more natural alignment was to improve patient outcome. The concept of kinematic alignment was reported in the United States with good early results.[37,38] In our study we used a comprehensive number of both joint specific and generic health scores (KOOS, AKSS, ULCA, SF-36 and EQ-5D) to assess outcome. We also used validated tests of function performed in a physiotherapy gymnasium. The theory behind this was that, although labour intensive to perform and record, these functional tests may give more subtle variations in the patient's performance pre- and post-operatively and allow more detailed functional assessment. However, despite this number of assessment tools no significant difference was demonstrated between kinematic and mechanical alignment.

The general trend was of significant improvement one year post-operatively in both groups compared to pre-operatively. There was a steady improvement in the ULCA, KOOS and SF-36 scores and the TUG and two minute walk tests during the post-operative period. This is in contrast to the quantifiably measured functions of ROM and peak torque in the hamstrings which decreased initially before improving. This could be attributed to pain relief as a consequence of the TKA resulting in an improved perception of function by the patient.

The peak torque in the quadriceps and hamstrings, and the functional component of the AKSS all showed a significant improvement in the first three months in the kinematically aligned group compared with the mechanically aligned group. Although this suggests an improved early recovery in the kinematically aligned group, there was no difference at one year.

In a similar randomised control trial of kinematic and mechanical alignment in TKA, Dossett et al[39,40] reported a significant improvement in the outcome in both groups at six months and two years post-operatively, but comparatively better function in the kinematic aligned group. They, however, used a different TKA (Vanguard, Biomet Inc. Warsaw, Indiana) and differing outcome measures, which may account for the contrasting results. There may also be differences in patient demographics between NHS patients in the United Kingdom and private patients in the United States, with differing expectations, which has been shown to affect outcome.[41] In the studies by Dossett et al,[39,40] the pre-operative scores were universally better in the kinematically aligned group than in the mechanically aligned group. A weakness of their study is that the accuracy of the cutting blocks was not assessed. Our study, however, and those of Dossett et al[39,40] represent robust level one evidence and although offer conflicting evidence, suggest that kinematic alignment is at least as good in terms of functional outcome as mechanical alignment. This supports the assertion that

Table V. Comparison of functional assessments one year post-operatively for the kinematically aligned group, comparing those within 3° of planned alignment and those outside 3° of planned alignment (incorrect)

		Planned KA (n = 26)		Incorrect KA (n = 7)			95% CI		
Functional assessment		Mean	SD	Mean	SD	Difference	Lower	Upper	p-value
UCLA		6.0	1.9	4.4	1.1	1.6	-0.2	3.4	0.82
KOOS		79.3	17.0	82.8	20.0	-3.4	-23.1	16.2	0.72
Function score		87.1	22.4	76.3	17.0	10.8	-14.3	35.9	0.38
PROM range		120.0	9.5	123.8	2.5	-3.8	-14.0	6.5	0.45
EQ5D-HS		81.0	12.6	77.0	8.4	4.0	-8.3	16.3	0.51
Pain score post		1.6	1.8	1.3	1.2	0.3	-2.3	2.9	0.81
TUG time		9.4	8.3	10.3	1.6	-0.9	-9.7	7.9	0.83
2 min distance		146.2	51.7	110.0	14.1	36.2	-18.5	90.9	0.18
Peak Tq quads		88.1	33.9	51.9	8.6	36.2	0.2	72.3	0.05
Peak Tq hams		44.3	18.0	28.0	7.9	16.3	-3.1	35.7	0.10
SF-36	PF	72.4	23.3	46.7	27.0	25.7	2.8	48.6	0.03
	RP	70.2	27.9	60.4	22.9	9.8	-15.9	35.6	0.44
	RE	82.5	24.1	72.2	26.7	10.3	-13.2	33.8	0.37
	SF	46.4	10.6	45.8	17.1	0.6	-11.0	12.2	0.92
	MH	62.6	11.6	65.0	11.8	-2.4	-13.5	8.7	0.66
	EV	49.7	13.3	52.1	7.6	-2.4	-14.2	9.4	0.68
	Pain	39.0	33.3	52.1	29.0	-13.1	-45.1	18.8	0.40
	GH	53.1	12.3	50.8	11.1	2.3	-9.2	13.8	0.69
	CH	28.6	25.4	29.2	29.2	-0.6	-25.5	24.4	0.96

KA, kinematically aligned; MA, mechanically aligned; CI, confidence interval;SD, standard deviation; UCLA, University of California, Los Angeles; KOOS, Knee Injury And Osteoarthritis Outcome Score; PROM, patient-reported outcome measure; EQ, EuroQol; TUG, timed up-and-go; Tq, torque; quads, quadriceps; hams, hamstrings; SF, short-form; PF, Physical Health; RP, Role-Physical; RE, Role-Emotional; SF, Social Functional; MH, Mental Health; EV, Emotional Vitality; GH, General Health; CH, Change Health

accurately recreating mechanical alignment does not necessarily correlate with improved outcome.[14]

Our study has limitations. Small deviations from the desired alignment may have affected the outcome, although the cutting blocks were at least as accurate as the intra- and extra-medullary guides in the mechanically aligned group. It is possible that a type II error could have occurred if the kinematically aligned group did not vary significantly in their alignment in comparison with the mechanically aligned group.

Follow-up at one year has been shown to predict long-term functional outcome,[42] but longer-term review is required to assess if kinematic alignment will have an effect on function and survivorship. This is particularly true for the outliers in the kinematically aligned group, where three patients had valgus alignment of > 6°. We recruited an unselected cohort of patients which was not powered to assess specific subgroups that may benefit from kinematic alignment. The pre-operative deformity in the kinematically aligned group ranged from 7° varus to 7° valgus, which is representative of most knees with osteoarthritis. We did not include knees with a deformity of > 10° and therefore adopting kinematic alignment for those with a complex deformity would require further investigation.

There were no catastrophic failures in the kinematically aligned group, as may have been feared from the some of the early literature on alignment.[10] Theoretically trying to reproduce more naturally aligned TKAs appears to be a logical progression in an attempt to improve the outcome. However, this randomised control trial failed to demonstrate any discernible difference between TKAs implanted in kinematic or mechanical alignment. Mid- to longer-term follow-up is required to confirm the equivocal functional outcome and that survival of the TKA is not compromised by kinematic relative to mechanical alignment.

Take home message:

The principle of trying to improve patient function in total knee arthroplasty by adhering more closely to individual patient anatomy appears to be a logical step with the improved survivorship of modern implants. This study, however, failed to demonstrate any discernible differences in outcome, therefore any further use of kinematic alignment should be undertaken in a controlled research environment.

Author contributions:
H. B. Waterson: Data collection, Analysis, Writing the paper.
N. D. Clement: Data analysis, Writing the paper.
K. S. Eyres: Performed surgeries, Reviewed the paper.
V. I. Mandalia: Performed surgeries, Reviewed the paper.
A. D. Toms: Data collection, Performed surgeries, Helped write and correct paper.

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FEATURE

H. B. Waterson, J. R. A. Phillips, FRCS (T&Orth)
V. I. Mandalia, A. D. Toms
Exeter Knee Reconstruction Unit, Royal Devon and Exeter Hospital, Exeter, UK
e-mail: hbwaterson@gmail.com

'Thou shalt not commit varus':
still applicable in total knee arthroplasty?

Mechanical alignment has been a fundamental tenant tenet of Total total Knee knee Arthroplasty arthroplasty (TKA), since modern knee replacement surgery was developed in the 1970's. The objective of mechanical alignment was to infer the greatest biomechanical advantage to the implant to prevent early loosening and failure. Over the last 40 years a great deal of innovation in TKA technology has been focusing on how to more accurately achieve mechanical alignment. Recently the concept of mechanical alignment has been challenged, and other alignment philosophies are being explored with the intention of trying to improve patient outcomes following TKA.

EVOLUTION OF ALIGNMENT CONCEPTS

Anatomists started detailing the morphology of the knee in the mid 1800s. The concept of improving lower limb alignment through osteotomy can be traced back to 1875 when Volkmann wrote on tibial osteotomies to improve a deformity of the knee.[1]. Zuppinger carried out the first radiological study of the knee in 1904 (Fig. 1).[2] Early osteotomies concentrated on straightening the leg and distributing load symmetrically across the joint. Debeyre and Patte were the first to report on a series of corrective osteotomies in osteoarthritis of the knee, concluding that they redistributed the load across the joint.[3]

By the mid twentieth century, radiographs were becoming more widespread in clinical work, and consequently the bony morphology could be visualised and various angles around the knee could be measured. The term 'femorotibial angle' was coined as the measurement of the intersection in the coronal plane of the long axis of femur and tibia at the knee joint and today is often referred to as the tibiofemoral angle (Fig.2). This angle gained popularity in knee osteotomies as a way of determining the degree of correction. The first published paper in the UK to reference the femorotibial angle in osteotomies was by Jackson and Waugh in 1961, [4] and they measured

DIE

AKTIVE FLEXION

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UNBELASTETEN KNIEGELENK.

VON

HERMANN ZUPPINGER,

ZÜRICH.

Mit 17 Textfiguren und 12 Figuren auf Tafel 22/33.

Fig. 1 Zuppinger's early manuscript containing early radiographic studies of the knee. Reprint with permission from X[2]

50 healthy knees and found the femorotibial angle on average to be 2˚. Kettelkamp et al[5] later disputed this figure in 1976 and suggested that the normal femorotibial valgus angulation was 7˚, which is more in line with what we accept today.

The concept of the mechanical axis was introduced around the same time in Maquet's 'Quelques remarques sur les radiographies'.[6] Alignment correction operations (osteotomies) were being planned on the basis of measurements made from full length radiographs of the affected leg, taken with the patient balancing on that extremity demonstrating an angle formed by the mechanical axis of the femur, connecting the centre of the femoral head and the intercondylar notch and the mechanical axis of the tibia between the tibial spines and the centre of the ankle.

Early techniques for knee arthroplasty were being developed around the same time as lower limb osteotomies were being popularised. The first metallic mould was introduced into the knee as a primitive form of arthroplasty by Campbell in 1940,[7] and attempts were made to correct alignment with acrylic tibial plateau prostheses by MacIntosh in 1958,[8] although it was not really until the 1970s that prototypes recognisable as similar to the TKAs in use today were developed. The early condylar total knee designs of the 1970s fell into two broad categories; the anatomic approach and the functional approach. The anatomic approach was based on preservation of the soft-tissue constraints

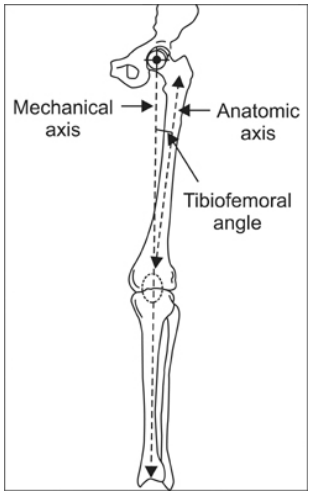

Fig. 2 The relationship between the mechanical and anatomic axis demonstrating the Tibiofemoral angle.

with replacement or resurfacing of the articular surface. The Gunston polycentric knee[9] was an example of an anatomical knee, as was the UCI knee,[10] but with more constrained implants, replicating the femoral condyles and tibial plateaux using casting techniques.

In the case of the Gunston polycentric knee arthroplasty,[9] it was designed to simulate opposing joint surfaces by separate implants for each joint surface. Collateral and cruciate ligaments were both retained to maintain joint stability. The polycentric knee reported to provide significant relief of pain in 86% of 500 knees, and the independence and activity levels of the patients increased dramatically. It was used predominantly in rheumatoid arthritis, however, it was prone to failure because the patellofemoral joint was not addressed and dislocation and subluxations were common as a consequence of ligamentous laxity in the presence of unbalanced soft tissues. To further compound the problems, high rates of loosening of the tibial components were also seen.[11,12] The stumbling block with these anatomical designs at the time were that these complex geometries were difficult to manufacture, the surgery was technically demanding, and deformity correction was not always possible without extensive soft-tissue resection.

The alternative to the anatomical approach was the functional approach, whereby the mechanics of the knee were simplified by resection of the condyles and the cruciate ligaments so the implant could be seated on a flat cancellous bone surface. The concept of the mechanical axis used in osteotomies was taken and used as a guide for implanting the prostheses.

Freeman stated in his implant design objectives[13] that the prosthetic component should be fitted to the bone by a means that spread the load over the largest possible area of the bone prosthesis interface. Instruments were designed to assist alignment and for checking the balance of the knee. Functional knee replacements ignored the natural obliquity of the joint (the lateral distal femoral angle and medial proximal tibial angle (Fig. 3)[14] in favour of a flat surface for the implant to sit on (Fig. 4).

Success in knee arthroplasty has long been measured by the survivorship of the implant. This was no different in the 1970s, and at this stage the functional approach was yielding improved survivorship over the anatomic approach, thus implants such as the Gunston quickly became obsolete.

'THOU SHALT NOT VARUS'

As mechanical alignment became the gold standard, clinical studies began to examine the correlation between position of the TKA and clinical outcome and survivorship. An early example of this was Lotke and Ecker in 1977,[15] examining 76 TKAs between 1972 and 1974. Short knee radiographs were compared with a knee evaluation index and revealed a strong correlation between good positioning of the prosthesis and good early clinical results, although there was no statistically significant correlation of mechanical failure and radiograph alignment scores.

One of the first large series comparing alignment and outcome in the same type of knee implant was by Hood, Vanni and Insall in 1981,[16] measuring tibiofemoral angles on short leg films before and after implantation of Insall-Burstein knee replacements in 225 patients (tibiofemoral valgus of 7° +/- 5°deemed satisfactory). Of the three failures, none were outside the limits that Hood had chosen.

In 1983 Bargren and Blaha[17] initiated a biomechanical study to assess the effects of eccentric loading on tibial component failure using the Freeman Swanson implant. The clinical outcome with relation to alignment in patients with the same implant using the small area tibial component between 1971 and 1975 was also reviewed. Taking into consideration that 1° to 13°of tibiofemoral valgus was deemed satisfactory, they found that 91% of the varus knees failed, 100% of the neutral knees failed and 11% of the valgus knees failed, demonstrating that the functionally designed early TKAs also had poor survivorship, even if the prostheses were implanted in the desired alignment. Tew and Waugh[18] picked up the subject again in 1985, pointing out that although the relationship between alignment and failure may have seemed too obvious to need substantiating, there was little evidence to support it. Their paper reviewed 428 TKAs of six different designs between 1972 and 1983 and found that those in extremes of varus and valgus did have significantly higher rates of failure.

Interest in the association between coronal alignment of the TKA and failure gathered momentum through the course of the 1990s. A number of clinical papers were published looking at prostheses predominantly implanted in

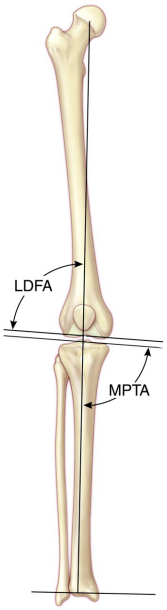

Fig. 3 Lateral Distal Femoral Angle (LDFA) and Medial Proximal Tibial Angle (MPTA), demonstrating the natural joint line obliquity. Reprinted with permission from [14]

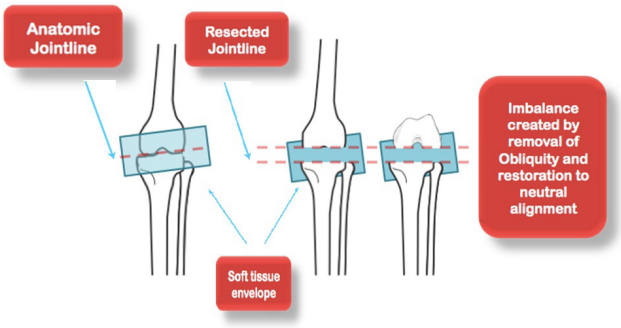

Fig. 4 A cut perpendicular to the mechanical axis. Ignoring the natural joint line obliquity creates a soft-tissue imbalance.

the 1970s to 1980s,[19,20] suggesting that deviation from the mechanical axis would lead to premature failure, leading to the now commonly expressed adage 'thou shalt not varus'. It is worth considering at this stage a number of important factors. These studies were examining functional TKAs that were designed to be implanted on a flat surface. Long leg radiographs were not commonplace and most of the studies had examined coronal alignment on short knee films. The correlation between tibiofemoral angle from knee radiographs and the mechanical axis obtained from full-limb radiographs ranges from 0.65 to 0.88.[21-23] Also, only one aspect of the multifaceted complex issue of alignment was being investigated; that of coronal alignment in extension. Little or no attention was being paid to alignment in the sagittal and axial planes, and how this might contribute to failure, or indeed soft-tissue balance and level of the joint line.

Research in the late 1990s shifted slightly from the simple relationship between coronal alignment and failure to trying to quantify the mode of failure. In 1999 a correlation between alignment and wear was established by Miura et al.[24] A tibial retrieval analysis of 89 Depuy PFC TKRs implanted between 1984 and 1998 by Collier et al[25] found shelf age of the polyethylene, patient age and varus alignment of greater than 5° all independently contributed to increased medial polyethylene wear. Biomechanical evidence suggested that varus tibial alignment led to increased posteromedial tibial surface strain in cadaver and knee simulator studies.[26-29]

The relationship between coronal mechanical alignment and its association with survivorship had built a weight of evidence and this in turn led to innovations in ways of more accurately reproducing mechanical alignment. Improvements with intra- and extramedullary guidance jigs enhanced the reproducibility of achieving overall mechanical alignment in the coronal plane, however, rotational alignment still relied on interpretation of anatomical landmarks.

THE MODERN ERA: IMPROVED ACCURACY OF ALIGNMENT? IMPROVED SURVIVORSHIP? IMPROVED PATIENT SATISFACTION?

By the end of the 1990s, TKAs were achieving better patient satisfaction, improved function and > 90% implant survival at 15 years.[30-32] The development of crosslinking UHMWPE was shown to reduce rates of wear in the hip[33] and was now being translated to the knee.[34]

Computer navigation (CN) was introduced as a new technology with the potential to further increase the accuracy of alignment,[35] enabling quantification of alignment parameters in multiple planes, but on the premise that increased accuracy would result in increased survivorship and outcome.

The advent of CN led to the publication of numerous trials utilising the technology. Meta-analysis of studies using CN suggested that improved accuracy of desired alignment is achieved using the technique.[35]

There has also been renewed debate as to whether the more modern implants with improved wear characteristics do fail earlier if a degree of deviation from mechanical alignment exists; the evidence is conflicting. Morgan et al[36] in 2008 published a series of 197 Kinemax knees implanted from 1990 to 1993 with a mean follow-up of nine years and was unable to demonstrate any difference in revision rates between alignment groups.

Following on from an article in 1994 (19), Ritter [37] published results in 2009 to re-establish the importance of mechanical alignment. This was a continuation of his work with Berend[38]. This study used multiple different versions of the AGC 6070 implants from 1983 to 2006. Short knee radiographs were used for measurements. The failure rate out with neutral alignment from 2.4° to 7.2° tibiofemoral valgus was found to be significantly higher and as with his previous paper (it was largely the same cohort of patients) varus failure was mostly due to medial tibial collapse. This was in response to research published by Parratte et al.[39] Parratte analysed 398 knee implants between 1985 and 1990 with long leg alignment films and a 15-year follow-up. The results showed that there was no difference in revision rate between prostheses implants in neutral (mechanical alignment 0+/-3°) and those in misalignment. This has again been supported by recent research showing there doesn't appear to be a correlation between misalignment and clinical outcome following TKA.[40]

The last publication to date further adds to the ambiguity of the subject. Bonner et al[41] analysed a total of 501 TKAs divided into an aligned group with a neutral mechanical axis (± 3°) and a misaligned group where the mechanical axis deviated from neutral by > 3°. At 15 years' follow-up there was no significant difference in revision for aseptic loosening between the two groups.

The literature on alignment and implant survivorship encompasses a huge diversity and evolution of implant and polyethylene designs over the last 40 years. There is a large variation in study methodology and analysis. Implants fail for a variety of reasons and the more recent literature would suggest that coronal alignment alone is not a good discriminator of implant longevity.

Regarding patient satisfaction, data from the National Joint Registries Annual Report 2013[42] suggests that the majority of TKA have a > 95% survivorship at nine years. Perhaps more pertinent is the patient perception of their outcome following surgery. Of the 132,019 patients who had a primary knee operation in 2012/2013 with an associated patient-reported outcome measure entry, 16.4% described their outcome as fair or poor, compared with 8.2% of patients who underwent primary hip surgery.

CN has undoubtedly improved accuracy of desired alignment but what CN has not been able to adequately demonstrate is that achieving mechanical alignment improves patient satisfaction following the TKA.[43]

THE FUNCTIONAL VERSUS ANATOMICAL IMPLANT DEBATE REIGNITED

Accuracy of desired alignment is improving, survivorship is improving but, importantly, patient satisfaction in TKA remains disappointing compared with hip surgery. Belleman's recent work confirms the concept of constitutional varus. 'An important fraction of the normal population has a natural alignment at the end of growth of 3° varus or more (Fig. 5). Restoration of mechanical alignment to neutral in these cases may not be desirable and would be unnatural for them' (Fig. 6).[44]

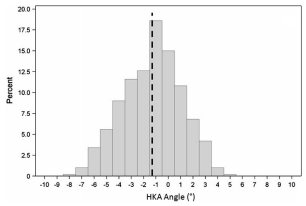

Fig. 5 Belleman's graph demonstrating the overall Hip Knee Ankle (HKA) axis in the general population is in overall varus. Reprinted with permission from X [44]

Fig. 6 A clear illustration of the variation in normal lower limb alignment.

The consequence of this ambiguity in the relationship between alignment and outcome has led to renewed interest in trying to achieve a more anatomical prosthesis akin to those made obsolete in the 1970s. The increasing use of more detailed imaging and computer software means it is now possible to critically look at alignment in three dimensions; this is the foundation for Patient Specific Instrumentation (PSI). CT and MRI scanning have enabled detailed three-dimensional pre- and post-operative assessment of the knee joint, which in turn has enabled custom PSI instrumentation. PSI offers the opportunity to accurately quantify alignment in every plane for the individual patient, and the cutting guides not only set the appropriate coronal orientation, but also the depth of resection, rotation, slope and flexion and extension axis based on the pre-operative template.

The majority of PSI manufacturers produce the guides to accurately create neutral mechanical lower limb alignment. Some companies, however, are now using this imaging technology to create a template to implant the TKA prosthesis in a position that is more anatomical (Stryker Shapematch). This is supposed to recreate the alignment of the patient's limb in their pre-arthritic state, taking into consideration natural individual variation in the alignment of the normal knee.[45] There has been recent research that has suggested that there is a single flexion-extension axis about the distal femur bisecting the femoral condyles but it does not correspond exactly to that of the epicondylar axis (Fig. 7).[45] With the use of MRI or CT for pre-operative planning, this flexion-extension axis can be defined by creating a single axis through the femoral condyles (Fig. 8)[46] and the PSI could then be produced to recreate it.

Similarly the ConforMIS iTotal system is designed to cut the femur and tibia perpendicular to the mechanical axis but then aims to recreate the natural joint line by building in obliquity, if necessary, to both the tibial polyethylene and condyles of the femoral implant.

The advent of PSI, CN and more modern, wear resistant implants has re-opened the debate that was started in the 1970s regarding functional and anatomical implants. The reasons for ignoring the normal anatomy of the knee have changed slightly 40 years on. Complex geometries are now easier to manufacture and the surgery is less technically demanding. What remains an unknown at present is whether patient satisfaction will improve or survivorship of the implant will be compromised if the current generation of prostheses are designed in a more anatomical position. 'Thou shalt not varus'- only time will tell.

Fig. 7 Three-dimensional knee model construction, illustrating the difference between with epicondylar (yellow) and cylindrical (green) axes. Reprinted with permission from X.[46]

Fig. 8 A cylinder is superimposed onto the femoral condyle to define a single flexion and extension axis. Reprinted with permission from X.[45]

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Appendix B: Conference presentations

EFORT. Prague 2015.

Waterson HB, Eyres K, Mandalia VI, Toms AD. Mechanical alignment compared to kinematic alignment in total knee arthroplasty: A prospective randomised double-blind study.

South-West Orthopaedic Club. Exeter May 2015.

Waterson HB, Eyres K, Mandalia VI, Toms AD. The outcome of total knee arthroplasty implanted in mechanical alignment compared to kinematic alignment: A prospective randomised double-blind study.

BASK. Telford March 2015.

Waterson HB, Clement N, Mandalia VI, Toms AD. The outcome of total knee arthroplasty implanted in mechanical alignment compared to kinematic alignment: A prospective randomised double-blind study.

BOA Birmingham Oct 2013

Waterson HB, Mandalia, VI, Toms AD. Kinematically aligned total knee arthroplasty.

EFORT June 2013.

Waterson HB, Mandalia, VI, Toms AD. Kinematically aligned total knee replacement.

BASK. Leeds 2013.

Waterson HB, Mandalia, VI, Toms AD. Kinematically aligned total knee arthroplasty demonstrates superior results over mechanically aligned total knee arthroplasty in the early post-operative period.

BASK. Leeds 2013.
Waterson HB, Mandalia, VI, Toms AD. Implant position relative to the mechanical axis of the femur and tibia for the kinematically aligned total knee replacement.

BASK. Leeds 2013.

Waterson HB, Mandalia, VI, Toms AD. Effect of kinematic alignment on peri-prosthetic bone mineral density, after total knee arthroplasty.

7th Orthopaedic & Trauma Update. France January 28-31st 2013.

Waterson HB, Mandalia VI, Toms AD. Kinematic aligned TKA demonstrates superior results to mechanically aligned TKA in the short term. Podium presentation 7th Orthopaedic & Trauma Update. France January 28-31st 2013.

Striking a Balance: Kinematic Alignment and ShapeMatch Technology. 24/25th January, Lucerne, Switzerland.

Waterson HB, Mandalia VI, Toms AD. The Exeter experience of the ShapeMatch TKA.

Golden Jubilee Congress of the Asia Pacific Orthopaedic Association and 7th Congress of the Asia Pacific Knee Society (APKS). New Deli, India, October 2012.

Mandalia VI, Waterson HB. The Hip Knee Ankle (HKA) axis and implant position relative to mechanical axis of femur and tibia for kinematically aligned Total knee Replacement.

The British Association for Computer Assisted Orthopaedic Surgery meeting. Glasgow, April 2012.

Waterson HB. The Otismed experience.

British Association for Surgery of the Knee meeting. Derby, April 2012.

Waterson HB, Barnett AJ, Searle D, Stroud R, Toms AD. Excellent early outcome and economic benefits using ShapeMatch total knee replacement.

Appendix C: Statistical output

Table 7.1 Short form- 36 health and quality of life scores including all the demains

	KA		MA					
	Mean	SD	Mean	SD	Mean Difference	Lower	Upper	p-value
PF0	44.0	22.5	45.2	27.9	13.9	4.2	23.5	**0.01**
RP0	45.2	27.9	33.8	20.5	11.4	-0.4	23.2	0.06
RE0	75.0	29.0	69.4	33.8	5.6	-9.5	20.7	0.46
SF0	50.0	14.2	50.0	16.6	0.0	-7.4	7.4	1.00
MH0	61.4	11.5	62.6	10.5	-1.1	-6.5	4.2	0.67
EV0	52.1	10.9	48.5	11.7	3.7	-1.8	9.1	0.19
Pain0	64.6	22.8	74.6	21.2	-10.0	-20.6	0.6	0.06
GH0	48.0	13.8	52.1	10.7	-4.1	-10.1	1.9	0.18
CH0	53.6	19.3	60.3	20.5	-6.7	-16.3	2.8	0.17
PF6	51.0	22.7	48.8	21.0	2.2	-11.0	15.4	0.74
RP6	50.3	26.5	46.5	21.6	3.8	-10.6	18.3	0.60
RE6	74.2	30.6	76.7	30.7	-2.5	-21.0	16.0	0.79
SF6	45.6	9.3	45.0	10.2	0.6	-5.3	6.6	0.83
MH6	61.3	15.3	60.0	10.0	1.3	-6.4	8.9	0.74
EV6	50.0	9.9	53.0	8.1	-3.0	-8.4	2.4	0.27
Pain6	58.8	21.1	62.5	24.7	-3.8	-17.8	10.3	0.59
GH6	54.0	11.3	53.4	10.3	0.6	-5.9	7.1	0.85
CH6	40.0	18.8	37.0	21.8	3.0	-9.4	15.4	0.63
PF12	70.0	20.7	62.8	22.0	7.2	-5.2	19.6	0.25
RP12	71.6	18.6	60.2	26.4	11.4	-2.0	24.8	0.09
RE12	89.8	18.0	81.4	27.4	8.4	-5.4	22.1	0.23
SF12	50.6	8.2	46.6	10.3	3.9	-1.6	9.4	0.16
MH12	68.4	12.2	63.3	10.9	5.1	-1.6	11.9	0.13
EV12	53.4	10.5	51.7	8.2	1.7	-3.7	7.2	0.53
Pain12	32.7	22.2	40.6	26.1	-7.9	-22.6	6.8	0.28
Pain12	32.7	22.2	40.6	26.1	-7.9	-22.6	6.8	0.28
GH12	50.9	13.5	50.2	10.0	0.7	-6.1	7.6	0.83
CH12	33.0	17.9	31.5	27.4	1.5	-12.2	15.1	0.83
PF26	73.8	24.3	58.8	27.6	15.1	0.9	29.2	**0.04**
RP26	70.7	26.0	61.9	26.6	8.8	-5.5	23.1	0.22
RE26	87.2	23.0	76.4	23.0	10.7	-1.7	23.2	0.09
SF26	44.7	12.8	45.5	8.5	-0.8	-6.7	5.1	0.78
MH26	63.3	10.9	62.8	13.5	0.5	-6.2	7.2	0.88
EV26	51.4	11.6	52.4	11.0	-0.9	-7.1	5.2	0.76
Pain26	27.6	23.6	43.1	24.1	-15.5	-28.9	-2.0	**0.03**
GH26	49.4	11.2	52.3	13.2	-2.9	-9.6	3.8	0.39

CH26	31.7	24.0	32.1	24.4	-0.4	-13.7	12.8	0.95
PF52	73.8	24.0	68.5	24.8	5.3	-8.6	19.2	0.45
RP52	70.2	23.7	68.0	25.2	2.2	-11.7	16.1	0.75
RE52	88.1	21.0	79.2	23.6	9.0	-3.7	21.6	0.16
SF52	47.0	6.5	45.3	12.7	1.7	-4.1	7.4	0.56
MH52	66.0	10.3	62.7	9.8	3.3	-2.5	9.0	0.26
EV52	52.4	11.3	50.3	12.6	2.1	-4.7	8.9	0.53
Pain52	30.1	27.2	40.5	30.1	-10.4	-28.0	7.3	0.24
GH52	50.2	13.0	53.1	13.2	-2.9	-10.4	4.5	0.43
CH52	30.8	25.8	28.4	25.9	2.4	-12.7	17.4	0.75

Physical functioning (PF), Role functioning/physical (RP), Role functioning/emotional (RE), Energy/fatigue (EV), Emotional well-being (MH), Social functioning (SF), Pain, General health (GH), Health change (CH)

Graphs of outcome measures

Figure 7.1 Graph illustrating changes in SF-36 scores over time

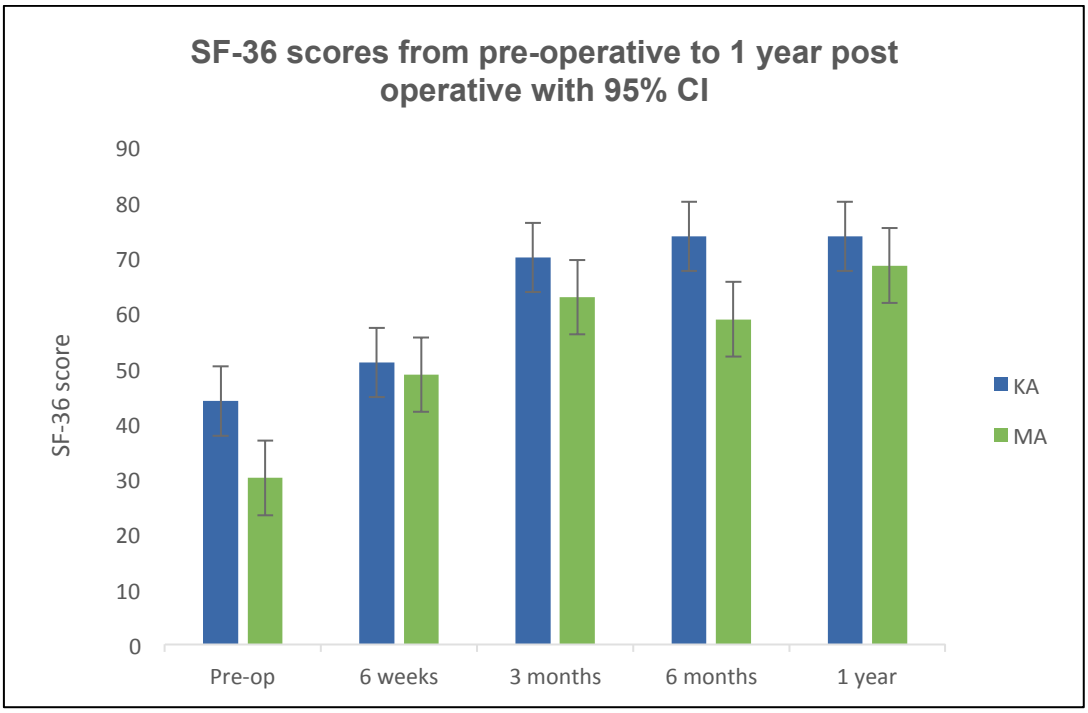


Figure 7.2 Graph illustrating changes in KOOS score over time

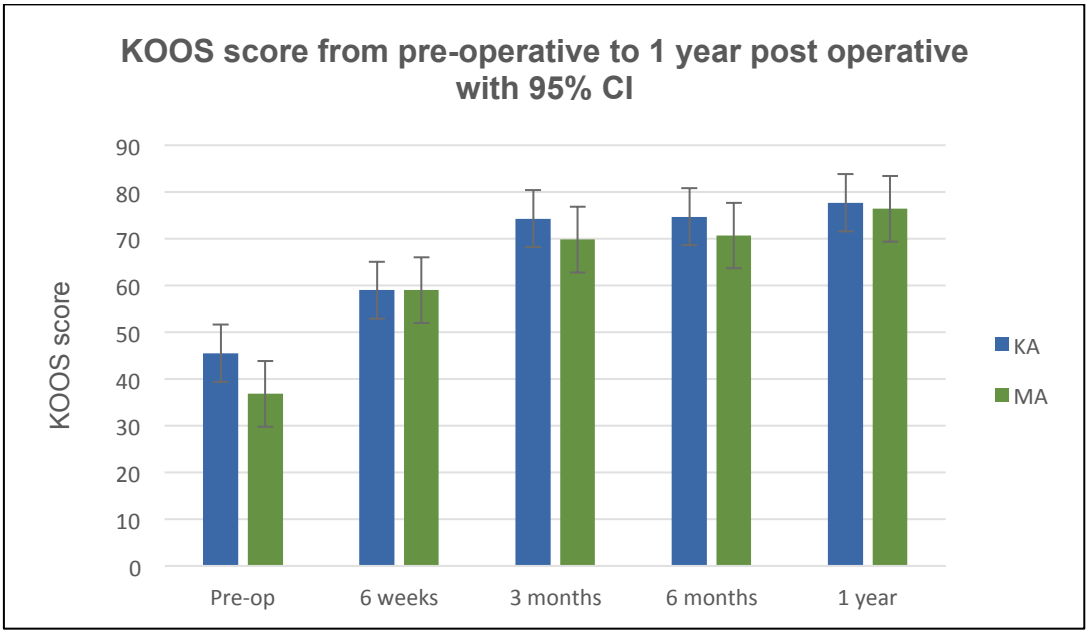


Figure 7.3 Graph illustrating changes in EQ-5D score over time

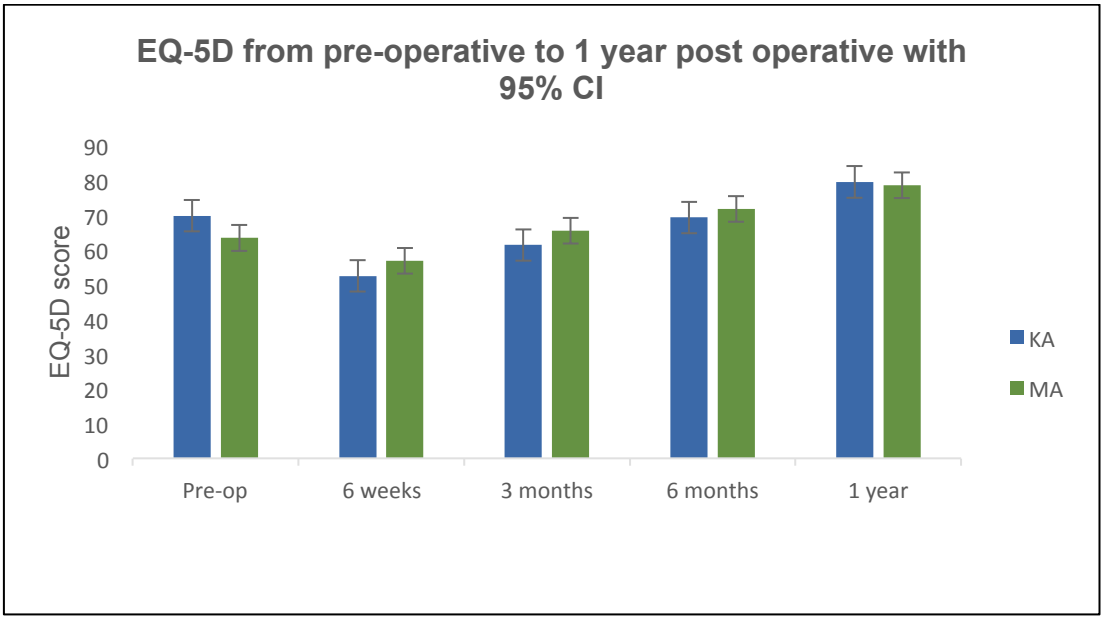


Figure 7.4 Graph illustrating change in UCLA score over time

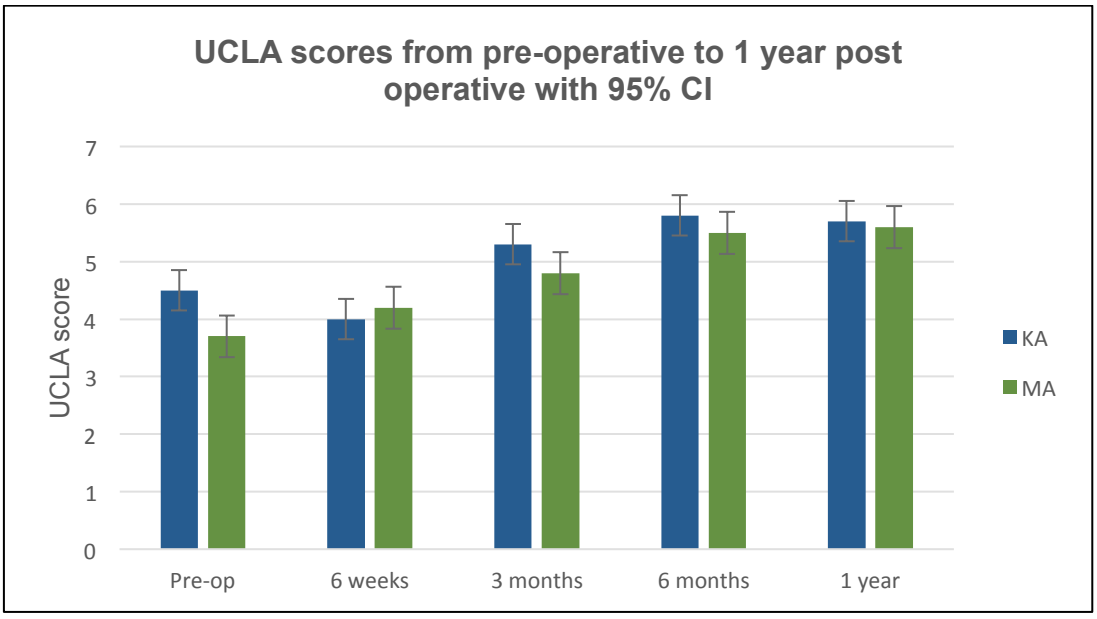


Figure 7.5 Graph illustrating change in AKSS over time

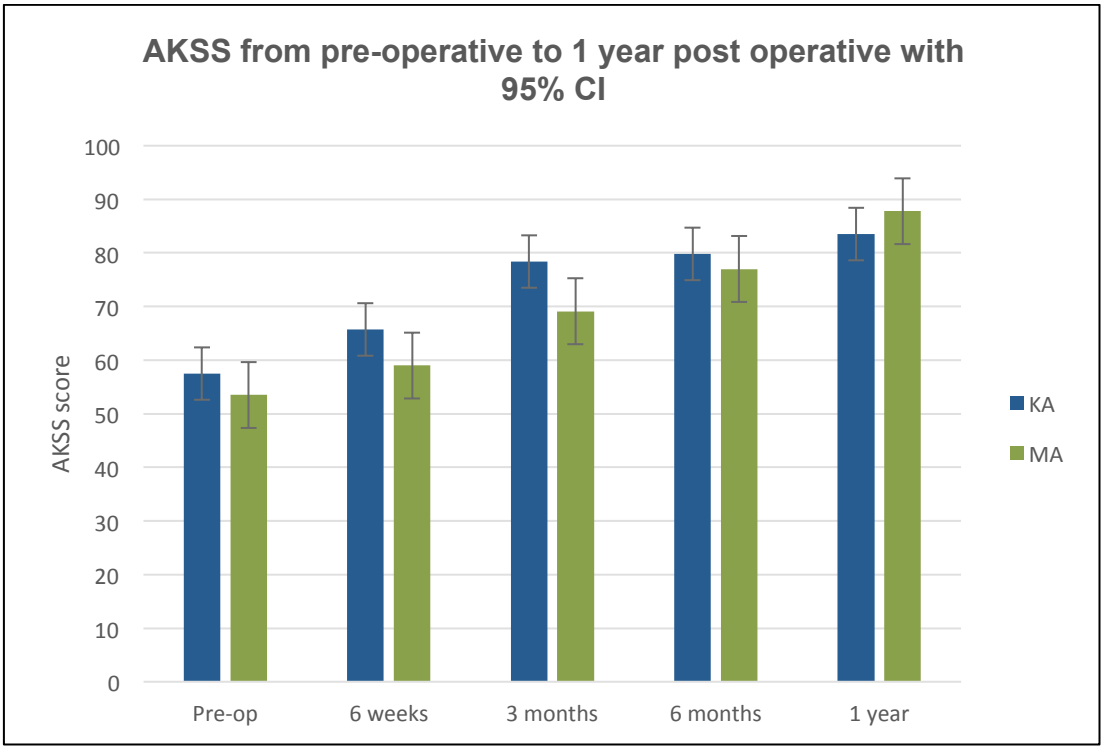


Figure 7.6 Graph illustrating changes in timed up and go test over time

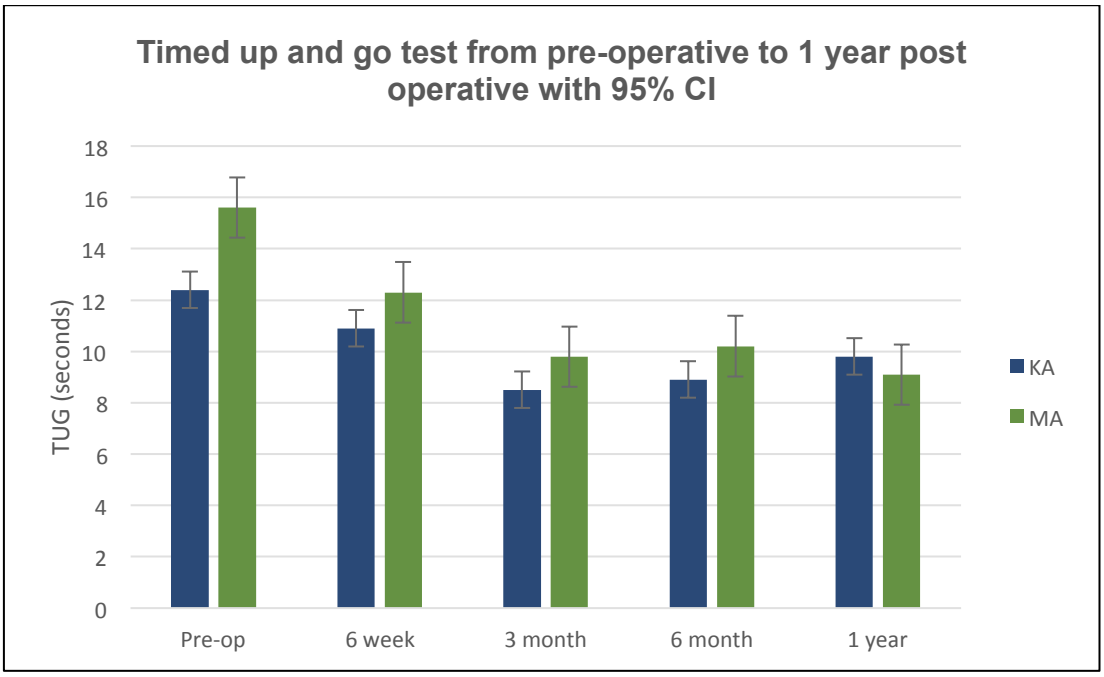


Figure 7.7 Graph illustrating changes in two minute walk test over time

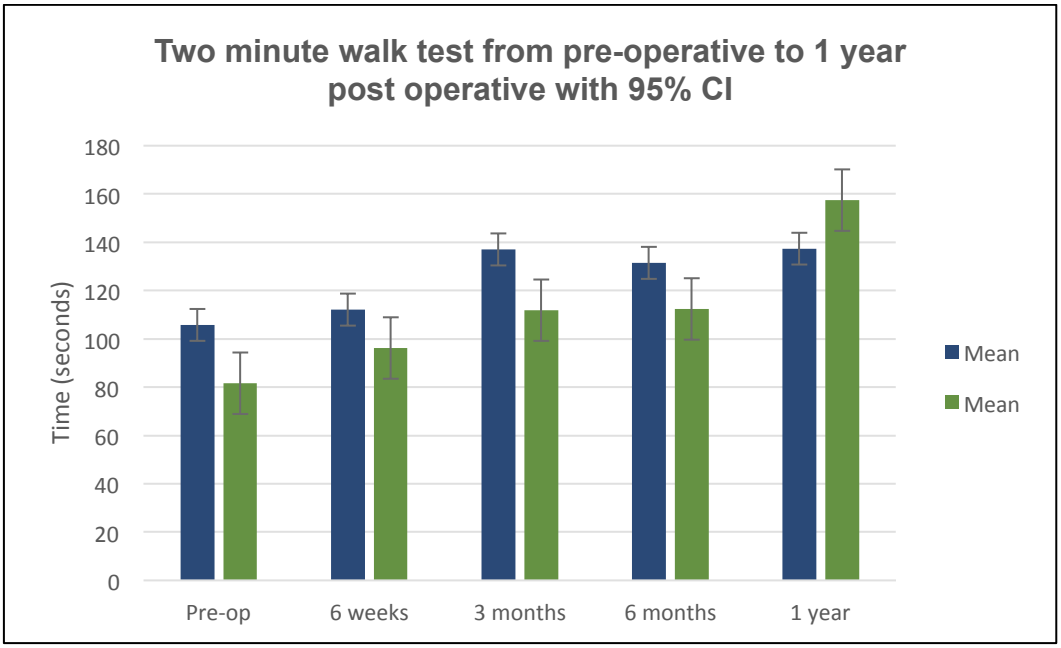


Figure 7.8 Graph illustrating changes in timed up and down stairs over time

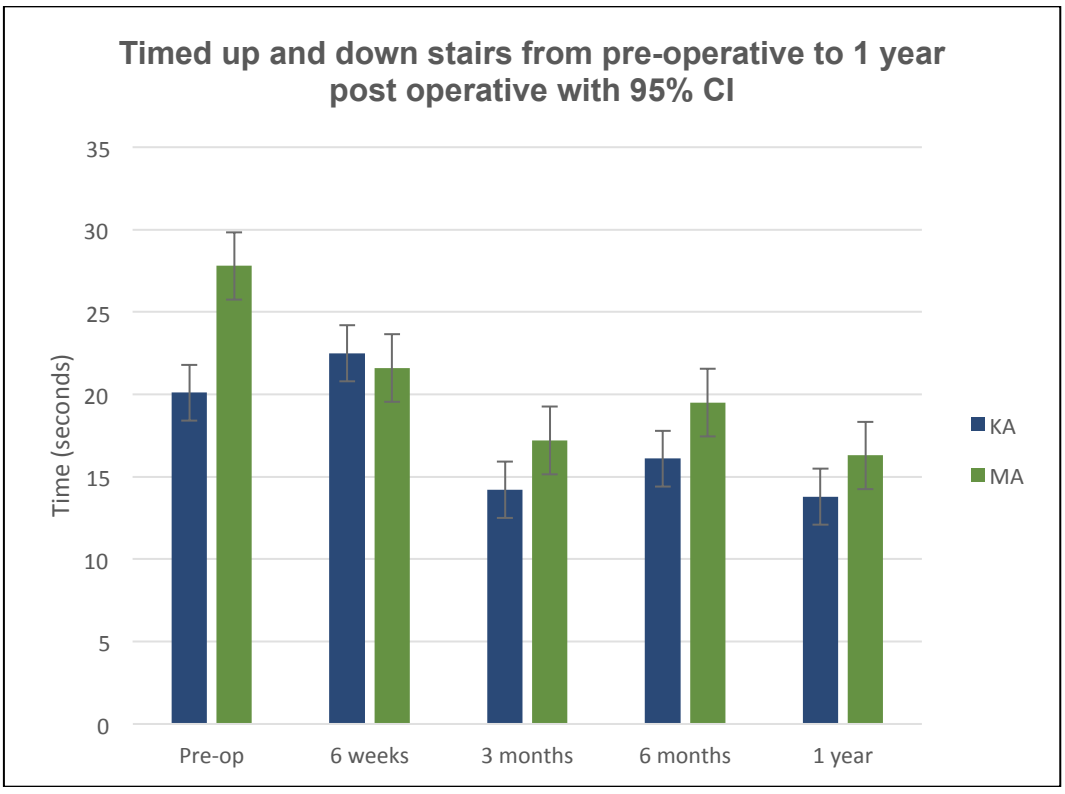


Figure 7.9 Graph illustrating changes in peak quadricep torque over time

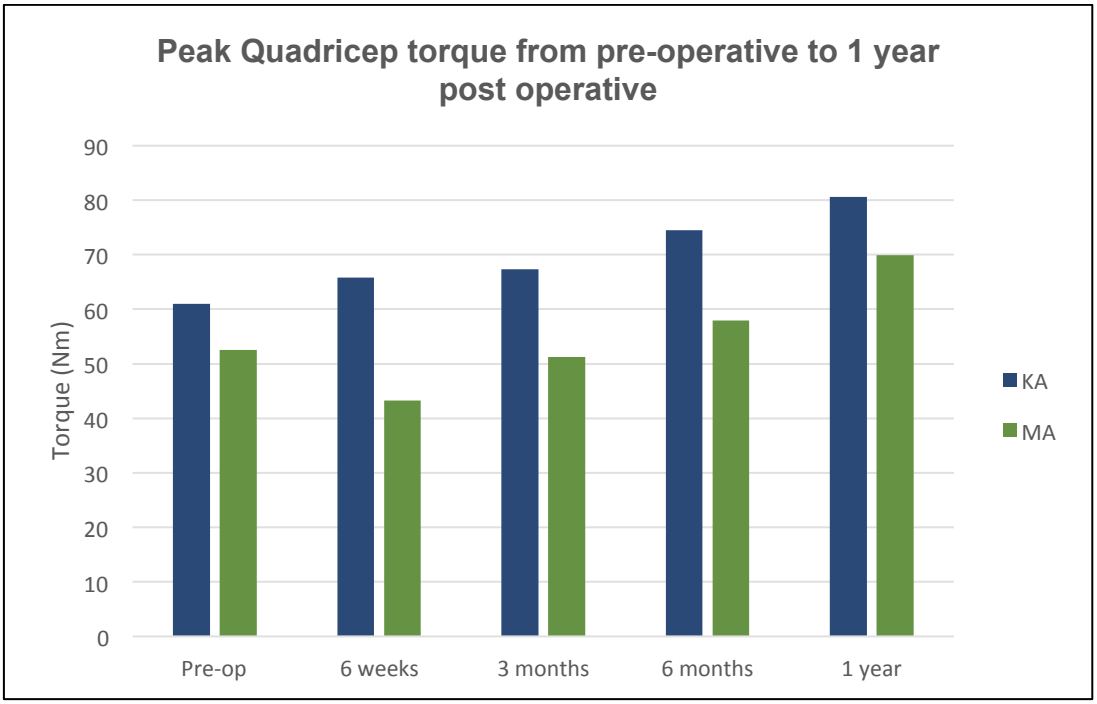
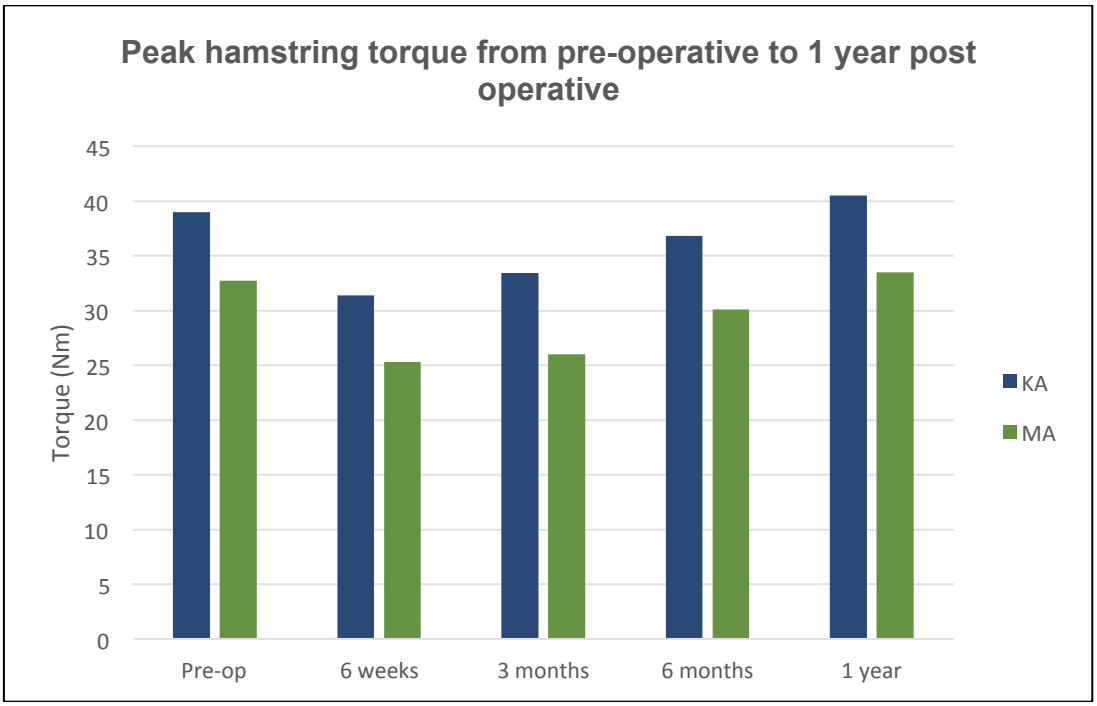


Figure 7.10 Graph illustrating changes in peak hamstring torque over time



Tables of further function tests

Table 7.2 illustrating changes in Wii fit balance scores over time

Wii fit	Mean KA	SD	Mean MA	SD	Mean Difference	Lower	Upper	p-value
Pre-op	70.4	22.5	73.6	16.8	-3.2	-12.9	6.4	0.50
6 weeks	76.8	11.0	73.6	19.6	3.2	-6.2	12.5	0.50
3 months	80.7	7.9	74.6	15.9	6.1	-1.2	13.5	0.10
6 months	74.6	17.1	74.9	11.2	-0.3	-7.9	7.2	0.93
1 year	77.4	13.7	74.2	11.1	3.2	-3.6	10.0	0.35

Table 7.3 illustrating changes in ability to kneel over time

Ability to kneel	OR	95% CI Lower	Upper	p-value
Pre-op	0.80	0.30	2.15	0.66
6 weeks	1.86	0.60	5.75	0.28
3 months	3.75	0.83	17.03	0.07
6 months	1.13	0.33	3.91	0.85
1 year	1.31	0.31	5.51	0.72

Table 7.4 illustrating changes in uphill treadmill gradient over time

	KA		MA		95% CI			
Gradient up treadmill	Mean	SD	Mean	SD	Mean Difference	Lower	Upper	p-value
Pre-op	11.5	5.6	10.5	4.9	1.0	-2.4	4.4	0.53
6 weeks	13.0	3.4	12.3	4.0	0.7	-1.5	2.9	0.55
3 months	14.8	1.1	13.2	3.6	1.5	-0.1	3.2	0.07
6 months	12.9	4.4	13.4	3.0	-0.5	-2.5	1.4	0.60
1 year	15.0	0.0	13.7	3.4	1.3	0.0	2.6	**0.05**

Table 7.5 illustrating changes in downhill gradient over time

Gradient down treadmill	KA		MA			95% CI		
	Mean	SD	Mean	SD	Mean Difference	Lower	Upper	p-value
Pre-op	9.3	6.2	10.0	5.4	-0.7	-4.4	3.1	0.72
6 weeks	12.1	3.9	11.6	4.6	0.5	-2.1	3.1	0.72
3 months	14.8	1.1	12.9	4.1	1.9	0.0	3.7	**0.05**
6 months	12.6	4.9	12.3	3.9	0.3	-2.1	2.6	0.82
1 year	15.0	0.0	14.3	2.1	0.7	-0.1	1.6	0.08

Table 7.6 illustrating changes in ability to walk over an uneven pebbled surface with time

Ability to walk on pebbles	KA		MA			95% CI		
	Mean	SD	Mean	SD	Mean Difference	Lower	Upper	p-value
Pre-op	3.5	3.5	4.9	2.7	-1.4	-3.5	0.7	0.15
6 weeks	1.9	2.7	1.5	2.1	0.4	-1.0	1.8	0.57
3 months	0.3	0.9	0.9	1.8	-0.6	-1.5	0.2	0.16
6 months	0.9	2.5	1.5	3.8	-0.6	-2.3	1.2	0.51
1 year	0.3	1.3	0.3	1.1	0.0	-0.7	0.6	0.91

Table 7.7 illustrating changes in pain scores over time

Pain scores	KA		MA		95% CI			
	Mean	SD	Mean	SD	Mean Difference		Lower	Upper	p-value
Pre-op	3.8	2.1	4.9	2.2	-1.1	0.5	-2.2	0.0	0.04
6 weeks	2.6	1.8	2.1	1.9	0.5	0.5	-0.6	1.6	0.36
3 months	0.8	1.0	1.8	2.1	-1.0	0.5	-2.0	0.1	0.08
6 months	1.0	1.3	1.1	1.4	-0.1	0.4	-0.9	0.7	0.85
1 year	2.0	2.2	1.9	1.1	0.1	0.9	-1.8	2.0	0.88

Table 7.8 illustrating changes in forgotten knee score over time

Forgotten knee		95% CI		
	OR	Lower	Upper	p-value
6 weeks	2.19	0.70	6.88	0.18
3 months	1.63	0.58	4.56	0.35
6 months	1.15	0.42	3.16	0.79
1 year	0.55	0.19	1.62	0.28

Tests for Normality

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Pre-opKOOS-QTotal	0.112	32	.200*	.948	32	0.127
6wKOOS-Total	0.079	32	.200*	.987	32	0.958
3mKOOS-Total	0.085	32	.200*	.970	32	0.496
6mKOOS-QTotal	0.154	32	.051	.927	32	0.031
1yKOOS-Total	0.132	32	.167	.901	32	0.007

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
preAKSS function score	0.136	29	.183	.941	29	0.109
6w AKSS Function score	0.258	29	.000	.853	29	0.001
3m ASKK function score	0.121	29	.200*	.931	29	0.060
6m ASKK function score	0.214	29	.002	.876	29	0.003
Function Score	0.280	29	.000	.784	29	0.000

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Pre-opEQ5D-HS	0.160	45	.006	.956	45	0.088
6wEQ5D-HS	0.220	45	.000	.786	45	0.000
3mEQ5D-HS	0.247	45	.000	.762	45	0.000
6mEQ5D-HS	0.234	45	.000	.757	45	0.000
1yEQ5D-HS	0.188	45	.000	.832	45	0.000

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Pre-opPROMRange	0.176	28	.027	.880	28	0.004
6wPROMRange	0.162	28	.058	.948	28	0.181
3mAROMRange	0.157	28	.074	.955	28	0.257
6mPROMRange	0.168	28	.042	.950	28	0.197
1yPROMRange	0.253	28	.000	.773	28	0.000

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Pre-opUCLA	0.191	28	.010	.928	28	0.054
6wUCLA	0.250	28	.000	.874	28	0.003
3mUCLA	0.209	28	.003	.898	28	0.010
6mUCLA	0.204	28	.004	.933	28	0.075
1yUCLA	0.164	28	.053	.938	28	0.096

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Pre-opTUGTime	0.168	32	.022	.731	32	0.000
6wTUGTime	0.169	32	.021	.905	32	0.008
3mTUGTime	0.163	32	.031	.894	32	0.004
6mTUGTime	0.128	32	.198	.912	32	0.013
1yTUGTime	0.139	32	.116	.921	32	0.022

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Pre-op2minDist	0.080	32	.200*	.989	32	0.977
6w2minDist	0.111	32	.200*	.973	32	0.578
3m2minDist	0.164	32	.029	.930	32	0.040
6m2minDist	0.185	32	.007	.896	32	0.005
1y2minDist	0.220	32	.000	.903	32	0.007

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Pre-opTimeUp&DownStairs	0.167	31	.027	.911	31	.014
6wTimeUp&DownStairs	0.143	31	.106	.835	31	.000
3mTimeUp&DownStairs	0.166	31	.029	.868	31	.001
6mTimeUp&DownStairs	0.173	31	.019	.830	31	.000
1yTimeUp&DownStairs	0.221	31	.000	.829	31	.000

a. Lilliefors Significance Correction

Appendix D: Protocols

Protocol for functional tests and evaluation schedule

Patient ID

Royal Devon and Exeter NHS
NHS Foundation Trust

FUNCTIONAL ASSESSMENT AFTER CONVENTIONAL KNEE ARTHROPLASTY& SHAPE MATCHED KNEE ARTHROPLASTY AND AMERICAN KNEE SOCIETY SCORE

Table 1. Evaluation schedule with detailed parameters:

	parameter	pre-op	per-op	ptd	diary						6 wk	3 mn	6 mn	1 yr
					week 1	week 2	week 3	week 4	week 5	week 6				
1	Medical history, length, body weight, gender, age, home situation	X												X
2	Operation report: ski-to-skin time, tourniquet time, stability, release, ligamnet quality		X											
3	Blood transfusion blood loss		X	X										
4	Drop of HB level pre-op versus ptd	X		X										
5	Drain production			X										
6	Hospital length of stay			X										
7	Complications		X	X							X	X	X	X
8	Routine X-ray	X		X							X	X	X	X
9	Long leg X-ray	X									X			
10	KOOS	X		X							X	X	X	X
11	UCLA	X		X							X	X	X	X
12	KSS	X		X							X	X	X	X
13	EQ-5D	X		X							X	X	X	X
14	SF-36	X		X							X	X	X	X
15	ROM active/passive	X		X	X	X	X	X	X	X	X	X	X	X
16	VAS pain rest/activity	X		X	X	X	X	X	X	X	X	X	X	X
17	VAS nausea	X		X	X	X	X	X	X	X				
18	Use of (pain) medication / morfine	X		X	X	X	X	X	X	X	X	X	X	X
19	Get-up-and-go-test	X		X	X	X	X	X	X	X	X	X	X	X
20	Knee swelling	X		X	X	X	X	X	X	X	X	X	X	X
21	Straight leg raise	X		X	X	X	X	X	X	X	X	X	X	X
22	Single leg stance more than 5 seconds	X		X	X	X	X	X	X	X	X	X	X	X
23	Ability to walk stairs normally with/without grab rails	X		X	X	X	X	X	X	X	X	X	X	X
24	Need for home care	X									X	X	X	X
25	Number of GP consultations										X	X	X	X
26	Frequency and number of physiotherapy										X	X	X	X
27	Resumption of work										X	X	X	X

Protocol for Function tests

1. Timed up and go test (TUG)- Patient rises from standard armchair, walks 3 meters at a comfortable safe pace, turns, walks back to the chair, and sits down.

Possible **Impossible**

0 1 2 3 4 5 6 7 8 9 10

2. The Two-minute walking test- Distance walked in 2 minutes measured in meters.

Possible **Impossible**

0 1 2 3 4 5 6 7 8 9 10

3. Timed stair- Ascending/descending steps in physio department x2 timed and scored on NAS.

Possible **Impossible**

0 1 2 3 4 5 6 7 8 9 10

4. Peak torque of quads and hamstrings measured on Digital Myometer?

Quads Moment Hamstring Moment

5. Wii Fit Yoga balance score both leg stance?

Possible **Impossible**

0 1 2 3 4 5 6 7 8 9 10

6. What is your ability to kneel?

Possible **Impossible**

0 1 2 3 4 5 6 7 8 9 10

7. How difficult did you find it walking up a slope on the treadmill?

Gradient **Speed**

Possible **Impossible**

0 1 2 3 4 5 6 7 8 9 10

8. How difficult did you find it walking down a slope on the treadmill?

Gradient **Speed**

Possible **Impossible**

0 1 2 3 4 5 6 7 8 9 10

9. How difficult did you find it walking across the pebbles?

Possible **Impossible**

0 1 2 3 4 5 6 7 8 9 10

10. What pain relief medication have you taken today and how much did you take?

11. What was your pain score before you took your pain relief?

No pain									severe pain	
0	1	2	3	4	5	6	7	8	9	10

12. What was your pain score after you took your pain relief?

No pain									severe pain	
0	1	2	3	4	5	6	7	8	9	10

13. Score with the Inertia-link?

Possible									Impossible	
0	1	2	3	4	5	6	7	8	9	10

14. Do you feel like you have forgotten that you have an artificial knee? Yes/No

13. Are you aware of your artificial joint?

Never almost never seldom sometimes mostly

Patient Reported Outcome Measures (PROM)

1. **UCLA** ☐
2. **SF-36** ☐
3. **EQ-5D** ☐
4. **KOOS** ☐
5. **KSS (The Knee Society Score filled in by staff)** ☐
6. **Forgotten knee Score** ☐

Appendix E: Ethical approval forms

NHS
Health Research Authority

NRES Committee South West - Exeter
South West REC Centre
Level 3
Block B
Lewins Mead
Whitefriars
Bristol
BS1 2NT

Telephone: 0117 342 1332
Facsimile: 0117 342 0445
e-mail: Ubh-tr.SouthWest2@nhs.net

01 May 2012

Mr Andrew Toms
Consultant Surgeon
RD&E NHS foundation trust
RD&E Hospital
Barrack Road
Exeter
Exeter EX2 5DW

Dear Mr Toms

Study title:	**A prospective, randomized, multi-centre study of the Triathlon Cruciate Retaining Total Knee System using ShapeMatched Cutting Guides**
REC reference:	**12/SW/0013**
Protocol number:	**K-S-045**

Thank you for your letter of 25 April 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		
Covering Letter		06 March 2012
Covering Letter		25 April 2012
Evidence of insurance or indemnity		20 May 2011
Investigator CV		19 September 2011
Letter from Sponsor		23 May 2011
Letter from Statistician		
Other: H. B. Waterson	1	01 October 2011
Other: instructions for use of medical device		
Other: Triathlon Express - protocol		
Participant Consent Form	1	23 May 2011
Participant Consent Form: OtisMead		23 May 2011
Participant Information Sheet	4	23 April 2012
Protocol	1	12 July 2011
Questionnaire: KOOS		
Questionnaire: EQ-5D		
Questionnaire: SF-36		
REC application	3.3	30 November 2011
Response to Request for Further Information		25 April 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/SW/0013	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Kirsten Peck.

Dr Denise Sheehan
Chair
NRES Committee South West - Exeter

Enclosures:	"After ethical review – guidance for researchers" [SL-AR2]
Copy to:	Mr Eric Garling, Stryker SA (eric.garling@stryker.com) Mr Andrew Toms, RD&E NHS foundation trust (Chris.gardner@rdeft.nhs.uk)

NHS
Health Research Authority

NRES Committee South West - Exeter

Bristol Research Ethics Committee Centre
Whitefriars
Level 3
Block B
Lewins Mead
Bristol
BS1 2NT

Tel: 0117 342 1332
Fax: 0117 342 0445
e-mail: Ubh-tr.SouthWest2@nhs.net

13 November 2012

Mrs Susan J Hopkins
PhD student
University of Exeter
University of Exeter, Physics Building
Stocker Road
Exeter
EX4 4QL

Dear Mrs Hopkins

Study title:	**A study into post-traumatic and post-surgical disuse osteopenia and its short- and long-term effects.**
REC reference:	**09/H0202/64**
Amendment number:	**3**
Amendment date:	**27 September 2012**

The above amendment was reviewed at the meeting of the Sub-Committee held on 09 November 2012.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Consent Form: Additional	1.0	21 September 2012
Participant Information Sheet: Additional	1.0	21 September 2012
Protocol	2.0 (tracked changes)	21 September 2012
Notice of Substantial Amendment (non-CTIMPs)		27 September 2012
Protocol	2.0 (clean copy)	21 September 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H0202/64:	**Please quote this number on all correspondence**

Yours sincerely

Kirsten Peck.

pp **Dr Denise Sheehan**
Chair
NRES Committee South West - Exeter

Enclosures:	List of names and professions of members who took part in the review
Copy to:	Ms Lynda Garcia, Royal Devon and Exeter NHS Foundation Trust (Dr Michael Wykes

Royal Devon and Exeter NHS
NHS Foundation Trust

Royal Devon and Exeter
Hospital (Wonford)
Barrack Road
Exeter
EX2 5DW

Tel: 01392 411611

GENERAL MANAGEMENT
Direct dial: 01392 406933
Direct Fax: 01392 403012
Email: Research@rdeft.nhs.uk
Ref: VP/MC/R&D/CG

Mr Andrew Toms
Consultant Orthopaedic Surgeon
Royal Devon & Exeter NHS Foundation Trust
Barrack Road
Exeter
EX2 5DW

17th November 2011

Dear Andrew

Study Title: **Functional assessment after conventional knee arthroplasty & shaped matched knee arthroplasty**

R&D Study No: **1205651** **MREC No:** **11/EE/0393**

I have reviewed the Trust R&D file for your study which has received approval from the Cambridge East Research Ethics Committee dated 09th November 2011. I am happy to give approval on behalf of the Royal Devon & Exeter NHS Foundation Trust (RD&E).

The documents approved with this study are detailed on the separate sheet.

Adverse Events

ALL **Serious Adverse Events (SAEs)** that occur to RD&E patients during the study must be reported to the R & D Office **within 24 hours** of becoming aware of the event. This must be done using the Trust R&D SAE fax template, quoting the study reference number.

Monitoring

You will be required to submit to the R&D Office regular quarterly updates on recruitment figures and an **End of Study Report** on completion of the trial at this site. If the study takes longer than 1 year, annual reports on progress will be needed. Any publications arising from the research conducted at this site must be sent to the R&D Office at Noy Scott House as part of the ongoing Research Governance process.

Research Governance

All research must be managed in accordance with the requirements of the **Department of Health's Research Governance Framework (RGF).** In order to ensure that research is carried out to these standards and to provide assurance to the Trust, your study may be randomly selected for audit at any time and you must co-operate with the auditors.

It is recommended that **Good Clinical Practice** (GCP) training is undertaken and updated every 2 years for those staff who will be consenting participants into the study.

It is the responsibility of the Lead investigator (Chief Investigator for locally initiated studies and Principal Investigator for Multi-Centre studies) to ensure clarity of roles and responsibilities and to make sure all study specific duties are appropriately delegated on the Delegation Log and signed/dated where appropriate.

Royal Devon and Exeter NHS
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The duration of the Trust Approval extends to the date specified in the IRAS application form. Action may be taken to suspend Trust Approval if the research is not run in accordance with the Research Governance Framework. Research must commence within 6 months of Trust R&D Approval.

With best wishes for a successful study

Yours sincerely

Dr Vaughan Lewis / Mr Martin Cooper
JOINT MEDICAL DIRECTORS

Cc
Mr Ben Waterson – Research fellow
R&D Study File

Trust approval Non-CTIMP V1.0 16/08/10